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Friedel-Crafts chemistry: Part 41. A new facile synthesis of indeno[1,2-c] pyrazoles, 2*H*-benzo[*g*]indazoles and benzo[6,7]cyclohepta[1,2-c]pyrazoles via Friedel-Crafts ring closures

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ABSTRACT

Expedient and novel alternative synthesis of some fused heteropolycycles containing pyrazole moiety is described. A series of indeno[1,2-*c*]pyrazoles, 2*H*-benzo[*g*]indazoles and benzo[6,7] cyclohepta[1,2-*c*]pyrazoles were prepared by Friedel-Crafts ring closure of suitable synthesized carboxylic acids and alkanols in the presence of $AlCl_3/CH_3NO_2$ or P_2O_5 or PPA (polyphosphoric acid) catalysts. The precursor acids were obtained by utilizing $KMnO_4$ oxidation of the corresponding aldehyde, alkylations of diethyl malonates and Perkin type approaches, whereas starting alkanols were smoothly obtained by reaction of carboxylic acid ester with Grignard reagent. To exemplify, cyclizations of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid (6) were accomplished using the above catalysts afforded 3-chloro-2-phenylindeno[1,2-*c*]pyrazol-4(2*H*)-one (1b). Similarly, cyclization of the 2-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)propan-2-ol (8) by a Friedel–Crafts-type ring closure afforded the 3-chloro-2,4-dihydro-4,4-dimethyl-2-phenylindeno[1,2-*c*]pyrazole (1a).

1. Introduction

The synthesis of pyrazoles and their condensed scaffolds have been a subject of consistent interest because of their long history of application in pharmaceutical [1-3] and agrochemical [4-6] industries.

Over the past two decades, pyrazole-containing compounds have received considerable attention owing to their diverse chemotherapeutic potentials. They display a broad spectrum of biological activities such as antimicrobial [7], antifungal [8], anti-inflammatory [9], antitumor [10], antihyperglycemic [11], analgesic [12], antipyretic [13], antibacterial [14], sedative-hypnotic [15], antidepressant [16], anti-rheumatoid arthritis [17], anticonvulsant [18], antipsychotic [19], antileukemic [20] and as HIV integrase inhibitor [21] agents. Also pyrazole derivatives were present in numerous herbicides [22], fungicides [23], insecticides [24], pesticides [25] and dyestuffs [26]. In spite of they are rare in nature, the only natural pyrazole (1-pyrazolyl-alanine) was isolated from seeds of watermelons [27].

Although the discovery [28] of pyrazoles as antipyretic agents dated back to 1884, synthesis of pyrazole systems have been a prominent research objective for over a century and a variety of well-established synthetic methodologies are available in the literature. Of the methods developed, 1,3-dipolar cycloadditions of diazocompounds [29] or nitrilimines with alkynes [30] or alkenes [31,32], reaction of chalcones and hydrazines [33], reaction of enaminones with different aminoheterocycles [34], condensation of 1,3-diketones and hydrazines in the presence of an acidic catalyst [35] and coupling of terminal alkynes with hydrazine and carbon monoxide [36].

Among different condensed pyrazoles polycycles, indeno[1,2-*c*]pyrazole (**1**) [37,38], 2*H*-benzo[*g*]indazole (**2**) [39-41] and benzo[6,7]cyclohepta[1,2-*c*]pyrazole (**3**) [42] derivatives (Figure 1) are such molecules which have unique nitrogen-containing tricyclic structures are known to exert biological activities in many active pharmaceutical ingredients [43,44].

Literature survey revealed that limited numbers of strategies have been successfully applied in the synthesis of such **1**-**3** skeletons derivatives. However, all such reported methods were based on the addition of substituted hydrazines to suitable chalcones, β-diketones and α-keto-β-hydroxyesters.

In an alternative pioneering strategy, Li *et al.* [45] achieved the synthesis of scaffold **2** and variety of aza-polycyclic aromatic compounds via superelectrophilic cyclizations of alkenyl-substituted *N*-heterocycles with triflic acid (CF_3SO_3H).

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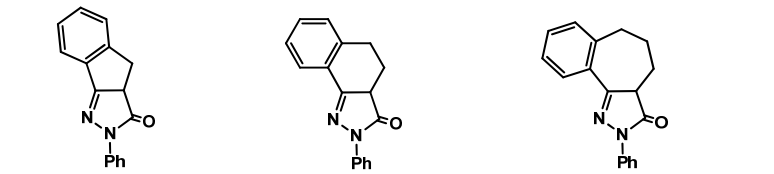


Figure 1. Pyrazole heteropolycycles containing pharmaceuticals.

The search for new methods for the simple, direct, concise, atom-economical synthetic route and efficient construction of this class of pyrazole compounds still constitutes a major challenge in organic synthesis.

In recent communications [46-50], we have demonstrated simple alternative procedures in the construction of novel and known heterocyclic systems proving the synthetic utility of Friedel-Crafts [51-54] cyclialkylation approach. The results manifested that a number of difficult heterocyclic skeletons can be easily prepared with the advantages of short reaction time and high yield. In view of the above reports and in continuation of our research in Friedel-Crafts ring closures, herein, we wish to report facile and efficient synthesis of substituted indeno[1,2-*c*]pyrazoles, 2*H*-benzo[*g*]indazoles and benzo[6,7] cyclohepta[1,2-*c*]pyrazole via Friedel-Crafts ring closures of heteroaryl acids and alkanols in the presence of both Brönsted and Lewis acid catalysts.

2. Experimental

2.1. Instrumentation

All reagents were purchased from Merck, Sigma or Aldrich Chemical Co. and were used without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus and are uncorrected. The IR spectra were determined with a Shimadzu 470 infrared spectrophotometer using KBr wafer and thin film techniques. The ^{1}H and ^{13}C NMR spectra were recorded on Jeol LA 400 MHz FT-NMR (400 MHz for ^{1}H, 100 MHz for ^{13}C) and on Varian NMR (90 MHz) spectrometers using $CDCl_3$ or DMSO-d_6 solvents with TMS as internal standard. Chemical shifts (δ) and *J* values are reported in ppm and Hz, respectively. Elemental analyses were performed on a Perkin-Elmer 2400 Series II analyser. The mass spectra were recorded on a JEOL JMS 600 spectrometer at an ionizing potential of 70 eV (EI) electron impact ionization mode using the direct inlet system. Reactions were monitored by thin-layer chromatography (TLC) using pre-coated silica plates and visualized with UV light. Flash column chromatography was performed on silica gel and basic alumina.

2.2. Synthesis

2.2.1. 5-Chloro-1,3-diphenyl-1H-pyrazole-4-carbaldehyde (5)

Pyrazolone **4** (4.7 g, 0.02 mol) was added in small portions over 5 min to an ice-cold Vilsmeier reagent prepared by slowly addition of $POCl_3$ (9.8 mL, 16.12 g, 0.1 mol) to DMF (17.8 mL, 16.8 g, 0.23 mol) at 0 °C over 30 min. The reaction mixture was heated for 3 h at 90 °C then cooled to 0 °C, poured into ice-cold water (100 mL) and finally treated with potassium carbonate till pH = 9. The separated yellow solid was filtered, dried and recrystallized from benzene to afford (4.4 g, 79 %) of pure aldehyde **5** (Scheme 1). Color: White crystals. M.p.: 107 °C (Lit. [55], M.p.: 109-111 °C). IR (KBr, ν, cm^{-1}): 3110, 3065 (CH) (Aromatic), 2830, 2745 (CH) (aldehyde), 1695 (C=O) (aldehyde), 1605, 1590, 1489, 1440 (C=C) (Aromatic), 1360, 1189, 716, 658. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 7.20-8.90 (m, 10 H, Ar-H), 10.30 (s, 1H, CHO). MS (EI, *m/z* (%)): 283 (M^++1, 45), 284 (M^++2, 28), 282 (M^+, 100), 254 (16), 253 (25), 248 (15), 220 (18), 77 (86), 51 (92). Anal. calcd. for $C_{16}H_{11}ClN_2O$: C, 67.96; H, 3.92; N, 9.91. Found: C, 68.25; H, 3.77; N, 9.90%.

2.2.2. 5-Chloro-1,3-diphenyl-1H-pyrazole-4-carboxylic acid (6)

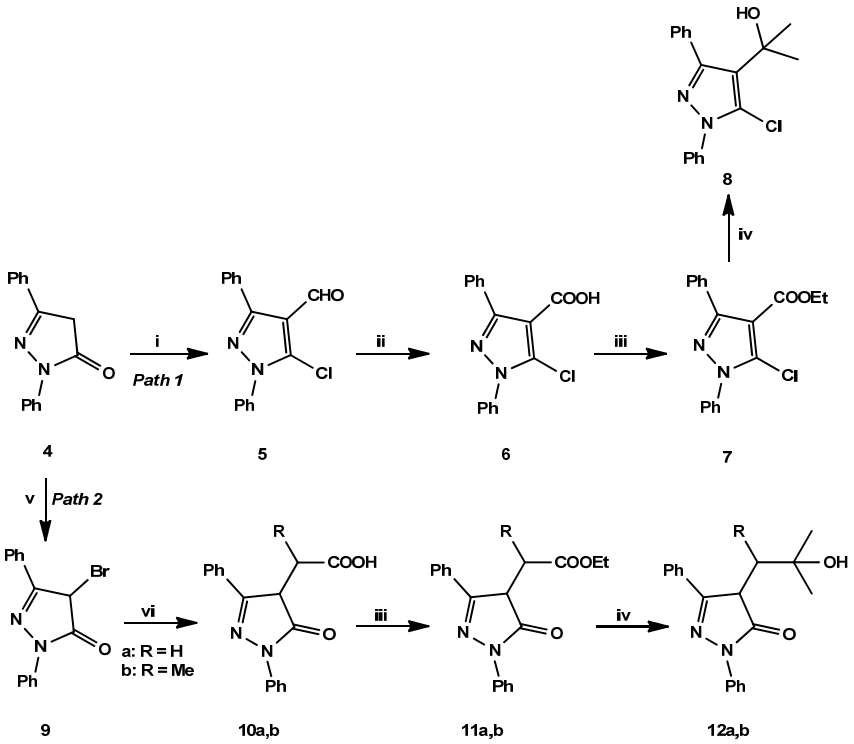
To a solution of compound **5** (4.2 g, 15 mmol) in a mixture of H_2O/*t*-butanol (1:1, 30 mL) was added a solution of $KMnO_4$ (3.3 g, 21 mmol) in H_2O (30 mL) at 70-80 °C over 2 h. Then an aqueous solution of KOH (10%, 30 mL) was added while stirring until the solution turned alkaline. The mixture was filtered and the clear filtrate was acidified with concentrated hydrochloric acid (20 mL, 30%) to pH = 2. The resulting precipitate was filtered, washed with water, dried and crystallized from ethanol to give (3.8 g, 85 %) of pure acid **6** (Scheme 1). Color: White crystals. M.p.: 183 °C. IR (KBr, ν, cm^{-1}): 3440 (OH) (acid), 3105 (CH) (Aromatic), 1690(C=O) (acid), 1610, 1585, 1473, 1440 (C=C) (Aromatic), 1360, 1140, 755. ^{1}H NMR (90 MHz, DMSO-d_6, δ, ppm): 7.60-8.70 (m, 10H, Ar-H), 11.20 (s, 1H, COOH). Anal. calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found; C, 64.52; H, 3.72; N, 9.33%.

2.2.3. 4-Bromo-1,3-diphenyl-1H-pyrazol-5(4H)-one (9)

To a an ice-cold solution of pyrazolone **4** (4.7 g, 20 mmol) in AcOH (30 mL) was added a solution of bromine (4.3 g, 27 mmol) in AcOH (10 mL) over a period of 10 min at 5-10 °C. The reaction mixture was stirred for 10 min, diluted with water (100 mL) over 5-10 min and left to stand in refrigerator for overnight. The solid was filtered, washed with AcOH (20 %) and dried. Crystallization from ethanol gave (4.6 g, 74 %) of pure bromopyrazolone **9** (Scheme 1). Color: Pale yellow needless. M.p.: 117 °C. IR (KBr, ν, cm^{-1}): 3090 (CH) (Aromatic), 2970 (CH) (pyrazole), 1678 (C=O) (amide), 1593, 1560, 1490, 1455 (C=C) (Aromatic), 1340, 1170, 745, 670. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 4.6 (s, 1H, CH), 7.45-8.50 (m, 10H, Ar-H). Anal. calcd. for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89. Found; C, 57.05; H, 3.55; N, 8.84%.

2.2.4. General procedure for the synthesis of substituted acids 10a,b

A solution of 4-bromo-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**9**) (4.7 g, 15 mmol) in 30 mL of dry benzene was added dropwise over 40 minutes to an ice-cold suspension of sodio-malonic ester prepared from sodium (1.0 g, 45 mmol) and substituted diethyl malonate (5.3 g, 33 mmol) in 30 mL of absolute ethanol. After complete addition, the reaction mixture was kept in a refrigerator for 24 h and then refluxed for 4 h. The solvents were evaporated and the resulting ester was refluxed for 2h with KOH solution (25 mL, 30 %). The mixture was diluted with water (30 mL), refluxed for an additional 1 h, cooled and acidified with HCl solution (40 mL, 30 %). The crude substituted malonic acid was filtered, washed with water and dried.



Reagents and conditions: (i) $POCl_3$/DMF, 90 °C, 3 h, K_2CO_3, (ii) $KMnO_4$, H_2O/*t*-butanol, 70-80 °C, 2 h, (iii) EtOH/H_2SO_4, 8h, reflux, Na_2CO_3, (iv) MeMgI, THF/Et_2O, rt, NH_4Cl soln (Table 1), (v) Br_2/AcOH, 5-10 °C, 20 min, (vi) (a) $NaCH(COOEt)_2$, KOH, 24 h, (b) heated at 190-200 °C.

Scheme 1

The acid was then heated at 190-200 °C in an oil bath with stirring for 20 minutes and the melt was poured into 20 ml of acetone. The acetone solution was treated with charcoal, warmed, filtered and the solvent was evaporated to afford crude acids. Crystallization from suitable solvents gave pure acids **10a**,**b** (Scheme 1). Analytical, physical and spectroscopic data are given in the following:

2-*(4,5-Dihydro-5-oxo-1,3-diphenyl-1H-pyrazol-4-yl)acetic acid* (**10a**): Color: Pale yellow crystals. Yield: 82%. M.p.: 124 °C (benzene). IR (KBr, ν, cm^{-1}): 3370 (OH) (acid), 3085 (CH) (Aromatic), 2950 (CH) (alkyl), 1720 (C=O) (acid), 1674 (C=O) (amide), 1610, 1590, 1460, 1445 (C=C) (Aromatic), 1335, 1180, 745. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 2.61 (t, 1Ha, *J* = 14.2 Hz, CH_2), 2.75 (t, 1Hb, *J* = 14.2 Hz, CH_2), 2.82 (app. t, 1H, *J* = 10.4 Hz, CH), 7.30-8.55 (m, 10H, Ar-H), 10.9 (s, 1H, COOH). Anal. calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found; C, 69.25; H, 4.56; N, 9.50%.

2-(4,5-Dihydro-5-oxo-1,3-diphenyl-1H-pyrazol-4-yl) propanoic acid (**10b**): Color: White crystals. Yield: 75%. M.p.: 95 °C (ethanol). IR (KBr, ν, cm^{-1}): 3355 (OH) (acid), 3075 (CH) (Aromatic), 2977(CH) (alkyl), 1715 (C=O) (acid), 1664 (C=O) (amide), 1600, 1585, 1450, 1440, 1380, 1130, 749. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 1.24 (d, 3H, *J* = 9.4 Hz, CH_3), 2.92 (p, 1H, *J* = 12.4 Hz, CH), 3.04 (app. q, 1H, *J* = 12.4 Hz, CH), 7.35-8.23 (m, 10 H, Ar-H), 11.6 (s, 1H, COOH). Anal. calcd. for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found; C, 70.05; H, 5.22; N, 9.26%.

2.2.5. General procedure for the synthesis of acids 13a,b

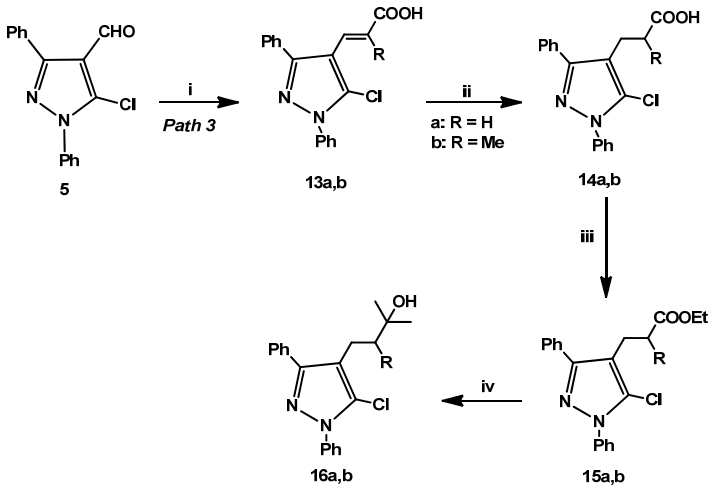
A mixture of aldehyde **5** (4.2 g, 15 mmol), acid anhydride (18 mmol) and sodium salt of the corresponding acid (18 mmol) was heated in an oil bath at 140-150 °C with occasionally stirring for 10-12 h. The warm mixture was poured with stirring into water (50 mL), basified with Na_2CO_3 solution (20 mL, 30%) and extracted with ether (2 × 20 mL). The ether extracts was discarded and the resulting solution was heated with decolorizing carbon (1 g), filtered while hot then it was poured with stirring into ice-cold concentrated hydrochloric acid chopped with ice (50 mL). After standing for overnight, the precipitated acids **13a** or **b** was filtered, washed successively with water and left to dry (Scheme 2). Purifications, yields and spectral data are given in the following:

(E)-3-(5-Chloro-1,3-diphenyl-1H-pyrazol-4-yl)acrylic acid (**13a**): Color: White crystals. Yield: 74%. M.p.: 156 °C (acetone). IR (KBr, ν, cm^{-1}): 3410 (OH) (br, acid), 3105 (=CH) (Alkene), 3060 (CH) (Aromatic), 2995 (CH) (alkyl), 1697 (C=O) (acid), 1600 (C=C) (Alkene), 1580, 1463, 1440 (C=C) (Aromatic), 1360, 1140, 745. ^{1}H NMR (90 MHz, DMSO-d_6, δ, ppm): 6.35 (d, 1H, *J* = 16.4 Hz, =CH), 7.20-8.10 (m, 10 H, Ar-H), 8.31 (d, 1H, *J* = 16.4 Hz, =CH), 11.2 (s, 1H, COOH). Anal. calcd. for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.62. Found; C, 66.49; H, 4.22; N, 8.64%.

(E)-3-(5-Chloro-1,3-diphenyl-1H-pyrazol-4-yl)-2-methyl acrylic acid (**13b**): Color: Pale yellow solid. Yield: 82%. M.p.: 172 °C (ethanol). IR (KBr, ν, cm^{-1}): 3410 (OH) (br, acid), 3094 (=CH) (Alkene), 3024 (CH) (Aromatic), 2975 (CH) (alkyl), 1700 (C=O) (acid), 1622 (C=C) (Alkene), 1588, 1450, 1440 (C=C) (Aromatic), 1385, 1145, 749. ^{1}H NMR (90 MHz, DMSO-d_6, δ, ppm): 1.83 (s, 3H, CH_3), 7.20-8.36 (11 H, m, Ar-H, =CH), 10.9 (1H, s, COOH). Anal. calcd. for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found; C, 67.30; H, 4.55; N, 8.40%.

2.2.6. General procedure for reduction of acids 14a,b

To a solution of acid **13a** or **13b** (10 mmol) in sodium hydroxide solution (15 mL, 1 N) was treated with sodium amalgam (25 g, 2.5%) in small portions over a period of 20 min with vigorous stirring.



Reagents and conditions: (i) (Ac_2O/AcONa) or (Pr_2O/PrONa)/140-150 °C, Na_2CO_3, 10-12 h, (ii) Na/Hg (2.5 %), NaOH, 5 h, (iii) EtOH/H_2SO_4, 8 h, reflux, Na_2CO_3, (iv) MeMgI, THF/Et_2O, rt, NH_4Cl solution (Table 1).

Scheme 2

The reaction mixture was stirred for additional 5 h at room temperature and then mercury was separated, washed with water and the washings were added to the main solution. The whole solution was acidified with concentrated HCl (10 mL) and the crude acid **14a** or **b** was filtered, washed with water and dried (Scheme 2). Yields and spectral data are given in the following:

3-(5-Chloro-1,3-diphenyl-1H-pyrazol-4-yl)propanoic acid (**14a**): Color: White needles. Yield: 92%. M.p.: 135 °C (ethanol). IR (KBr, ν, cm^{-1}): 3345 (OH) (br, acid), 3090(CH) (Aromatic), 2988(CH) (alkyl), 2490, 1720 (C=O) (acid), 1605, 1590, 1465, 1450(C=C) (Aromatic), 1350, 1165, 745. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 2.65 (t, 2H, *J* = 6.2 Hz, CH_2), 2.90 (t, 2H, *J* = 6.2 Hz, CH_2), 6.83-8.15 (10 H, m, Ar-H), 10.5 (1H, s, COOH). Anal. calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57. Found; C, 66.24; H, 4.64; N, 8.53%.

2-((5-Chloro-1,3-diphenyl-1H-pyrazol-4-yl)methyl)propanoic acid (**14b**): Color: Pale yellow solid. Yield: 86%. M.p.: 94 °C (ethanol). IR (KBr, ν, cm^{-1}): 3320 (OH) (br, acid), 3030 (CH) (Aromatic), 2975 (CH) (alkyl), 1715 (C=O) (acid), 1600, 1580, 1450 (C=C) (Aromatic), 1350, 1140, 755. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 1.10 (d, 3H, *J* = 10.4 Hz, CH_3), 2.63 (t, Ha, *J* = 16.3 Hz, CH_2), 2.73 (ddq, 1H, *J* = 9.3 Hz, -CH), 2.86 (dd, Hb, *J* = 16.3 Hz, CH_2), 6.90-8.25 (m, 10 H, Ar-H), 10.8 (s, 1H, COOH). Anal. calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found; C, 66.95; H, 4.85; N, 8.37%.

2.2.7. General procedure for the synthesis of ester 7 or 11a,b or 15a,b

A mixture of acid **6** or **10a**,**b** or **14a**,**b** (15 mmol), absolute ethanol (30 mL) and concentrated sulfuric acid (4 mL) was refluxed for 8 h. The excess alcohol was removed in *vacuo* and the resulting residue was poured into water (100 mL), basified by addition of solid Na_2CO_3 and left to stand for 3 h at refrigerator. The product was filtered, washed with water and dried to yield the crude esters. These products were subjected to flash column chromatography (basic alumina, EtOAc/*n*-hexane, 2/1) to give the pure esters **7** or **11a**,**b** or **15a**,**b** (Scheme 2). Yields, further purifications and spectral data are given in the following:

Ethyl 5-chloro-1,3-diphenyl-1H-pyrazole-4-carboxylate (**7**): Color: Pale yellow crystals. Yield: 90%. M.p.: 105 °C (benzene). IR (KBr, ν, cm^{-1}): 3070 (CH) (Aromatic), 2965 (CH) (alkyl), 1715 (C=O) (ester), 1600, 1585, 1490, 1440 (C=C) (Aromatic), 1340, 1230, 750. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 1.27 (t, 3H, *J* = 7.5 Hz, CH_3), 4.40 (q, 2H, *J* = 7.5 Hz, CH_2), 7.40-8.60 (m, 10H, Ar-H). Anal. calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57. Found; C, 66.27; H, 4.36; N, 8.56%.

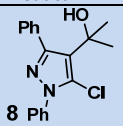
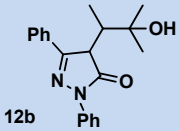
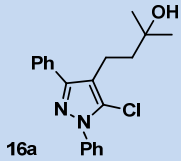
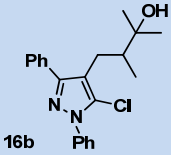
Ethyl 2-(4,5-dihydro-5-oxo-1,3-diphenyl-1H-pyrazol-4-yl) acetate (**11a**): Color: White plates. Yield: 88 %. M.p.: 142 °C (ethanol). IR (KBr, ν, cm^{-1}): 3083 (CH) (Aromatic), 2980 (CH) (alkyl), 1745 (C=O) (ester), 1682 (C=O) (amide), 1605, 1585, 1460, 1455 (C=C) (Aromatic), 1330, 1275, 745. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 1.32 (t, 3H, *J* = 7.5 Hz, CH_3), 2.62 (dd, 1Ha, *J* = 14.2 Hz, CH_2), 2.74 (t, 1Hb, *J* = 14.2 Hz, CH_2), 3.27 (t, 1H, *J* = 10.4 Hz, CH), 4.22 (q, 2H, *J* = 7.5 Hz, CH_2), 7.50-8.30 (m, 10 H, Ar-H). Anal. calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found; C, 70.83; H, 5.74; N, 8.49%.

Ethyl 2-(4,5-dihydro-5-oxo-1,3-diphenyl-1H-pyrazol-4-yl) propanoate (**11b**): Color: Reddish viscous oil. Yield: 89 %. $^{n}D^{25}$ = 1.644. IR (Film, ν, cm^{-1}): 3075 (CH) (Aromatic), 2977 (CH) (alkyl), 1740 (C=O) (ester), 1673 (C=O) (amide), 1600, 1585, 1495, 1455 (C=C) (Aromatic), 1340, 1245, 745. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 1.15 (d, 3H, *J* = 9.4 Hz, CH_3), 1.35 (t, 3H, *J* = 7.5 Hz, CH_3), 2.82 (p, 1H, *J* = 12.5 Hz, CH), 3.24 (app. t, 1H, *J* = 12.5 Hz, CH), 4.20 (q, 2H, *J* = 7.5 Hz, CH_2), 7.45-8.50 (m, 10 H, Ar-H). Anal. calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found; C, 71.44; H, 6.14; N, 8.09%.

Ethyl 3-(5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)propanoate (**15a**): Color: Yellowish viscous oil. Yield: 85 %. $^{n}D^{25}$ = 1.584. IR (Film, ν, cm^{-1}): 3055 (CH) (Aromatic), 2964 (CH) (alkyl), 1738 (C=O) (ester), 1590, 1550, 1460, 1430 (C=C) (Aromatic), 1335, 1265, 750. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 1.30 (t, 3H, *J* = 7.5 Hz, CH_3), 2.52 (t, 2H, *J* = 6.2 Hz, CH_2), 2.95 (t, 2H, *J* = 6.2 Hz, CH_2), 4.10 (q, 2H, *J* = 7.5 Hz, CH_2), 7.22-8.45 (m, 10 H, Ar-H). Anal. calcd. for $C_{20}H_{19}ClN_2O_2$: C, 67.70; H, 5.40; N, 7.89. Found; C, 67.91; H, 5.37; N, 7.90%.

Ethyl 2-((5-chloro-1,3-diphenyl-1H-pyrazol-4-yl)methyl) propanoate (**15b**): Color: Pale yellow crystals. Yield: 86 %. M.p.: 74 °C (ethanol). IR (KBr, ν, cm^{-1}): 3105 (CH) (Aromatic), 2985 (CH) (alkyl), 1742 (C=O) (ester), 1600, 1560, 1485, 1440 (C=C) (Aromatic), 1370, 1220, 747. ^{1}H NMR (90 MHz, $CDCl_3$, δ, ppm): 1.12 (d, 3H, *J* = 10.4 Hz, CH_3), 1.25 (t, 3H, *J* = 7.5 Hz, CH_3), 2.66 (q, Ha, *J* = 16.3 Hz, CH_2), 2.71 (ddq, 1H, *J* = 9.3 Hz, -CH), 2.94 (dd, Hb, *J* = 16.3 Hz, CH_2), 4.25 (q, 2H, *J* = 7.5 Hz, CH_2), 6.95-8.25 (m, 10H, Ar-H). Anal. calcd. for $C_{21}H_{21}ClN_2O_2$: C, 68.38; H, 5.74; N, 7.59. Found; C, 68.36; H, 5.69; N, 7.65%.

Table 1. Optimum conditions for the synthesis of heteroarylalkanols **8**, **12a**,**b** and **16a**,**b**.

Entry	Substrate	Product	Conditions [a]	Mp °C (n_D^{25})	Yield (%) [b]
1	7	 **8**	Et_2O/THF, rt, 8 h	92	8 (89)
2	11a	 **12a**	Et_2O/THF, rt, 6 h	(1.597)	12a (85)
3	11b	 **12b**	Et_2O/THF, rt, 8 h	84	12b (92)
4	15a	 **16a**	Et_2O, rt, 4 h	118	16a (90)
5	15b	 **16b**	Et_2O, rt, 5 h	(1.619)	16b (86)

[a] All reactions were performed using 0.4 equiv. excess of MeMgI.
[b] Isolated yield refer to substrate.

2.2.8. General procedure for the synthesis of alcohols 8, 12a,b, 16a,b

To an ice-cold Grignard reagent solution obtained as usual from Mg turnings (0.32 g, 13 mmol), alkyl or aryl halide (13 mmol) in ether (40 mL), was added a solution of esters **7** or **11a**,**b** or **15a**,**b** (4.6 mmol) in ether or THF (30 mL). The reaction mixture was stirred at required temperature for appointed time (Table 1) followed by decomposition with saturated aqueous NH_4Cl solution. The product was extracted with ether (3×30 mL) and the combined organic phases were washed with water, dried over anhydrous $MgSO_4$. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography (basic alumina, EtOAc:*n*-hexane, 3:1, *v*:v) resulting pure alcohols **8** or **12a**,**b** or **16a**,**b** (Scheme 2). The conditions and isolated yields are shown in Table 1 and spectral data are given in the following:

2-(5-Chloro-1,3-diphenyl-1H-pyrazol-4-yl)propan-2-ol (**8**): Color: White plates. Yield: 80 %. M.p.: 92 °C (cyclohexane). IR (KBr, ν, cm^{-1}): 3340 (OH) (alcohol), 3060 (CH) (Aromatic), 2975 (CH) (alkyl), 1610, 1560, 1450, 1445 (C=C) (Aromatic), 1375, 1330, 760. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.40 (s, 6H, $2CH_3$), 3.5 (s, 1H, OH exchangeable with D_2O) 7.50-8.60 (m, 10H, Ar-H). MS (EI, *m/z* (%)): 314 (M^++2, 6), 312 (M^+, 17), 310 (40), 294 (100), 277 (61), 253 (82), 235 (52), 194 (42), 180 (35), 177 (18), 168 (14), 158 (37), 103 (33), 91 (27), 77 (27). Anal. calcd. for $C_{18}H_{17}ClN_2O$: C, 69.12; H, 5.48; N, 8.96. Found; C, 69.31; H, 5.26; N, 8.82%.

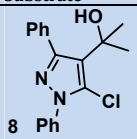
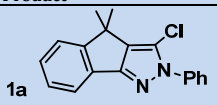
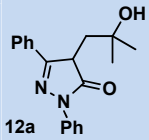
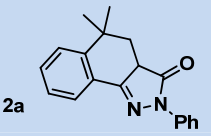
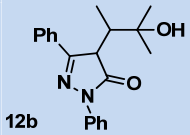
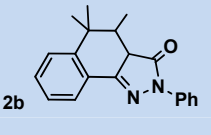
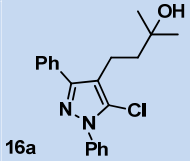
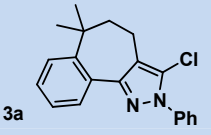
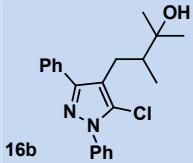
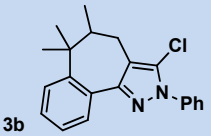
4-(2-Hydroxy-2-methylpropyl)-1,3-diphenyl-1H-pyrazol-5(4H)-one (**12a**): Color: Pale yellow viscous oil. Yield: 81 %. n_D^{25} = 1.597. IR (Film, ν, cm^{-1}): 3440 (OH) (alcohol), 3035 (CH) (Aromatic), 2970 (CH) (alkyl), 1665 (C=O) (amide), 1600, 1580, 1455, 1445 (C=C) (Aromatic), 1390, 1330, 745. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.30 (s, 6H, $2CH_3$), 1.74 (app. t, 2H, *J* = 14.2 Hz, CH_2), 2.55 (s, 1H, OH exchangeable with D_2O), 2.65 (t, 1H, *J* = 14.2 Hz, CH), 7.25-8.22 (m, 10H, Ar-H). MS (EI, *m/z* (%)): 308 (M^+, 13), 290 (100), 249 (55), 231 (41), 235 (55), 193 (20), 180 (29), 178 (15), 167 (11), 158 (35), 103 (24), 90 (22), 77 (44). Anal. calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found; C, 74.18; H, 6.40; N, 9.10%.

4-*(3-Hydroxy-3-methylbutan-2-yl)-1,3-diphenyl-1H-pyrazol-5(4H)-one* (**12b**): Color: Cream plates. Yield: 84 %. M.p.: 84 °C (benzene). IR (KBr, ν, cm^{-1}): 3425 (OH) (br, alcohol), 3060 (CH) (Aromatic), 2965 (CH) (alkyl), 1668 (C=O) (amide), 1594, 1580, 1455, 1440 (C=C) (Aromatic), 1385, 1320, 743. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.90 (d, 3H, *J* = 9.4 Hz, CH_3), 1.27 (s, 6H, $2CH_3$), 1.85 (p, 1H, *J* = 12.5 Hz, -CH), 2.10 (s, 1H, OH exchangeable with D_2O), 2.42 (d, 1H, *J* = 12.5 Hz, CH), 7.15-8.25 (m, 10H, Ar-H). MS (EI, *m/z* (%)): 322 (M^+, 10), 304 (100), 263 (31), 245 (75), 248 (62), 235 (33), 194 (37), 180 (20), 177 (14), 168 (21), 158 (48), 103 (23), 91 (35), 77 (47). Anal. calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found; C, 74.62; H, 6.69; N, 8.63%.

4-(5-Chloro-1,3-diphenyl-1H-pyrazol-4-yl)-2-methylbutan-2-ol (**16a**): Color: White needles. Yield: 85 %. M.p.: 118 °C (benzene). IR (KBr, ν, cm^{-1}): 3490 (OH) (alcohol), 3075 (CH) (Aromatic), 2990 (CH) (alkyl), 1610, 1490, 1455, 1430 (C=C) (Aromatic), 1386, 1355, 1020, 745. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.10 (s, 6H, $2CH_3$), 1.55 (t, 2H, *J* = 6.2 Hz, CH_2), 1.80 (s, 1H, OH exchangeable with D_2O), 2.40 (t, 2H, *J* = 6.2 Hz, CH_2), 7.22-8.30 (m, 10 H, Ar-H). MS (EI, *m/z* (%)): 342 (M^++2, 9), 340 (M^+, 22), 338 (48), 322 (100), 281 (51), 267 (42), 263 (12), 253 (70), 245 (38), 235 (18), 194 (42), 180 (11), 176 (19), 167 (30), 159 (43), 103 (13), 91 (38), 77 (39). Anal. calcd. for $C_{20}H_{21}ClN_2O$: C, 70.48; H, 6.21; N, 8.22. Found; C, 70.49; H, 6.26; N, 8.05%.

4-(5-Chloro-1,3-diphenyl-1H-pyrazol-4-yl)-2,3-dimethyl butan-2-ol (**16b**): Color: Reddish viscous oil. Yield: 81 %. n_D^{25} = 1.619. IR (Film, ν, cm^{-1}): 3465 (OH) (alcohol), 3055 (CH) (Aromatic), 2973 (CH) (alkyl), 1590, 1480, 1455, 1440 (C=C) (Aromatic), 1345, 745.

Table 2. Friedel-Crafts ring closures of heterocyclic alkanols **8**, **12a**,**b** and **16a**,**b**.

Entry	Substrate	Product	Conditions	Yield (%) [a]
1	 8	 1a	$AlCl_3/CH_3NO_2$[b], DCM[c],20 h, rt P_2O_5[d], Toluene, 8 h, reflux PPA[e], 4 h, 200-210 °C	86 75 72
2	 12a	 2a	$AlCl_3/CH_3NO_2$, DCM, 4 h, rt P_2O_5, PhH, 5 h, reflux PPA, 2 h, 180-190 °C	92 83 75
3	 12b	 2b	$AlCl_3/CH_3NO_2$, DCM, 4 h, rt P_2O_5, PhH, 3 h, reflux PPA, 2 h, 200-210 °C	85 80 76
4	 16a	 3a	$AlCl_3/CH_3NO_2$, DCM, 1 h, rt P_2O_5, PhH, 5 h, reflux PPA, 1h, 180-190 °C	83 79 74
5	 16b	 3b	$AlCl_3/CH_3NO_2$, DCM, 1 h, rt P_2O_5, PhH, 4 h, reflux PPA, 1 h, 200-210 °C	86 80 77

[a] Isolated yield refer to substrate.
[b] With $AlCl_3/CH_3NO_2$ catalyst reactant proportions were: carbinol or acid (0.002 moe), $AlCl_3$ (0.0024 mol), CH_3NO_2 (0.024 mol), solvent (10 mL).
[c] Dichloromethane.
[d] With P_2O_5 catalyst reactant proportions were: carbinol or acid (0.4 g) and P_2O_5 (4 g) in anhydrous toluene or benzene (15 mL).
[e] With PPA catalyst reactant proportions were: carbinol or acid (0.5 g) and PPA (5 g).

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.95 (d, 3H, *J* = 10.4 Hz, CH_3), 1.30 (s, 6H, $2CH_3$), 2,21 (dt, 1H, *J* = 9.3 Hz, -CH), 2.42 (t, Ha, *J* = 16.3 Hz, CH_2), 2.64 (app.t, Hb, *J* = 16.3 Hz, CH_2), 2.50 (s, 1H, OH exchangeable with D_2O), 7.22-8.15 (m, 10 H, Ar-H). MS (EI, *m/z* (%)): 356 (M^++2, 5), 354 (M^+, 13), 336 (100), 295 (74), 280 (48), 267 (35), 252 (84), 245 (24), 235 (13), 194 (48), 180 (14), 176 (26), 167 (35), 159 (52), 103 (15), 91 (48), 77 (42). Anal. calcd. for $C_{21}H_{23}ClN_2O$: C, 71.07; H, 6.53; N, 7.89. Found; C, 71.11; H, 6.53; N, 7.65%.

2.2.9. Friedel-Crafts cyclialkylations procedures

The procedures [46-54] described earlier for cyclialkylation of acids and alcohols with $AlCl_3/CH_3NO_2$ or P_2O_5 or PPA catalysts were essentially followed. In all reactions, the crude oily or solid products were purified by flash column chromatography (basic alumina, EtOAc:*n*-hexane, 3:1, *v*:*v*) gave the pure products **1a**,**b**, **2a-d** and **3a-d**. The conditions and yields for all products are shown in Table 2 and 3 while the physical and spectral data of the products are given below.

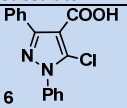
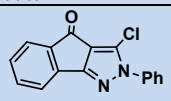
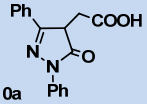
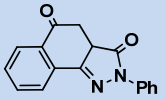
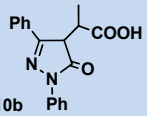
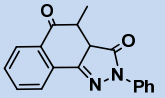
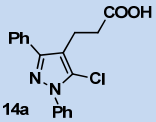
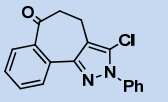
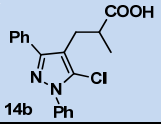
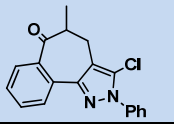
3-Chloro-2,4-dihydro-4,4-dimethyl-2-phenylindeno[1,2-c] pyrazole (**1a**): Color: White needles. M.p.: 117 °C (acetone). IR (KBr, ν, cm^{-1}): 3075 (CH) (Aromatic), 2980 (CH) (alkyl), 1600, 1480, 1460, 1435 (C=C) (Aromatic), 1355, 1220, 748. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.42 (s, 6H, $2CH_3$), 7.15-8.35 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 27.6 (1C, -*C*$(CH_3)_2$), 31.4 (2C, -C(*CH*$_3)_2$), 117.4 (1C, C-3a), 123.4 (2C, Ar., C-2', C-6'), 126.3 (1C, Ar., C-4'), 126.7 (1C, Ar., C-7), 127.4 (1C, Ar., C-5), 128.2 (1C, N-C(Cl)=, C-3), 129.2 (1C, Ar., C-8), 129.4 (1C, Ar., C-6), 132.4 (2C, Ar., C-3', C-5'), 134.7 (1C, Ar., C-8a), 142.7 (1C, Ar., C-1'), 156.1 (1C, N=C-, C-8b), 160.4 (1C, Ar., C-4a). Anal. calcd. for $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; N, 9.50. Found; C, 73.38; H, 5.14; N, 9.37%.

4,5-Dihydro-5,5-dimethyl-2-phenyl-2H-benzo[g]indazol-3 (3aH)-one (**2a**): Color: White needles. M.p.: 92 °C (acetone). IR (KBr, ν, cm^{-1}): 3090 (CH) (Aromatic), 2980 (CH) (alkyl), 1674 (C=O) (amide), 1600, 1475, 1465, 1440 (C=C) (Aromatic), 1350, 750. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.40 (s, 6H, $2CH_3$), 1.84 (t, 1Ha, *J* = 14.2 Hz, CH_2), 2.17 (dd, 1Hb, *J* = 14.2 Hz, CH_2), 2.35 (app. q, 1H, *J* = 10.4 Hz, CH), 6.85-8.11 (9H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 29.2 (2C, -C(*CH*$_3)_2$), 33.4 (1C, -*C*$(CH_3)_2$), 43.6 (1C, -CH_2-, C-4), 44.3 (1C, -CH-CO-, C-3a), 122.5 (2C, Ar., C-2', C-6'), 124.4 (1C, Ar., C-4'), 125.2 (1C, Ar., C-6), 126.4 (1C, Ar., C-9a), 127.6 (1C, Ar., C-8), 128.8 (1C, Ar., C-9), 131.4 (2C, Ar., C-3', C-5'), 133.7 (1C, Ar., C-7), 144.4 (1C, Ar., C-1'), 153.7 (1C, N=C-, C-9b), 157.5 (1C, Ar., C-5a), 178.2 (1C, C=O, C-3). Anal. calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found; C, 78.55; H, 6.37; N, 9.49%.

4,5-Dihydro-4,5,5-trimethyl-2-phenyl-2H-benzo[g]indazol-3(3aH)-one (**2b**): Color: Reddish viscous oil. n_D^{25} = 1.592. IR (Film, ν, cm^{-1}): 3062 (CH) (Aromatic), 2955 (CH) (alkyl), 1665 (C=O) (amide), 1590, 1490, 1470, 1445 (C=C) (Aromatic), 1345, 7453. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.10 (d, 3H, *J* = 9.4 Hz, CH_3), 1.37 (s, 6H, $2CH_3$), 2.21 (p, 1H, *J* = 12.5 Hz, CH), 2.38 (app. t, 1H, *J* = 12.5 Hz, CH), 7.19-8.35 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 14.2 (1C, -CH(*CH*$_3$)), 28.3 (2C, -C(*CH*$_3)_2$), 37.6 (1C, -*C*$(CH_3)_2$, C-5), 42.8 (1C, -*C*(CH_3), C-4), 44.2 (1C, -CO*C*H-, C-3a), 121.8 (2C, Ar., C-2', C-6'), 124.8 (1C, Ar., C-4'), 125.2 (1C, Ar., C-6), 126.7 (1C, Ar., C-9a), 127.2 (1C, Ar., C-8), 128.8 (1C, Ar., C-9), 132.2 (2C, Ar., C-3', C-5'), 133.4 (1C, Ar., C-7), 144.2 (1C, Ar., C-1'), 151.7 (1C, N=C-,C-9b), 157.5 (1C, Ar., C-5a), 181.3 (1C, C=O, C-3). Anal. calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found; C, 78.79; H, 6.44; N, 9.36%.

3-Chloro-6,6-dimethyl-4,5,6-trihydro-2-phenyl-benzo[6,7] cyclohepta[1,2-c]pyrazole (**3a**): Color: Reddish viscous oil. n_D^{25} = 1.589.

Table 3. Friedel-Crafts ring closures of heterocyclic acids **6** or **10a**,**b** or **14a**,**b**.

Entry	Substrate	Product	Conditions	Yield (%)
1	 6	 1b	$AlCl_3/CH_3NO_2$, DCM, 18 h, reflux P_2O_5,Toluene, 6 h, reflux PPA, 5 h, 210-220 °C	90 81 77
2	 10a	 2c	$AlCl_3/CH_3NO_2$, DCM, 10 h, reflux P_2O_5, Toluene, 6 h, reflux PPA, 4 h, 190-200 °C	89 82 73
3	 10b	 2d	$AlCl_3/CH_3NO_2$, DCM, 8 h, reflux P_2O_5, Toluene, 3 h, reflux PPA, 2 h, 200-210 °C	81 89 79
4	 14a	 3c	$AlCl_3/CH_3NO_2$, DCM, 8 h, reflux P_2O_5, Toluene, 5 h, reflux PPA, 2h, 190-200 °C	92 82 79
5	 14b	 3d	$AlCl_3/CH_3NO_2$, DCM, 4 h, reflux P_2O_5, Toluene, 4 h, reflux PPA, 2 h, 200-210 °C	88 81 80

IR (Film, ν, cm^{-1}): 3090 (CH) (Aromatic), 2980 (CH) (alkyl), 1604, 1485, 1465, 1442 (C=C) (Aromatic), 1350, 695. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.27 (s, 6H, $2CH_3$), 1.75 (t, 2H, *J* = 6.2 Hz, CH_2), 2.64 (t, 2H, *J* = 6.2 Hz, CH_2), 7.21-8.14 (9H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.5 (1C, -CH_2-, C-4), 31.5 (2C, -C(*CH_3*)$_2$), 42.6 (1C, -*C*(CH_3)$_2$, C-6), 49.2 (1C, -CH_2-, C-5), 119.3 (1C, C-3a), 122.4 (2C, Ar., C-2', C-6'), 125.6 (1C, Ar., C-7), 125.8 (1C, Ar., C-10a), 126.2 (1C, Ar., C-9), 126.8 (1C, Ar., C-4'), 127.4 (1C, N-C(Cl)=, C-3), 127.8 (1C, Ar., C-10), 128.4 (1C, Ar., C-8), 131.2 (2C, Ar., C-3', C-5'), 142.7 (1C, Ar., C-1'), 149.1 (1C, Ar., C-6a), 154.5 (1C, N=C-, C-10b). Anal. calcd. for $C_{20}H_{19}ClN_2$: C, 74.41; H, 5.93; N, 8.68. Found; C, 74.23; H, 6.08; N, 8.46%.

3-Chloro-5,6,6-trimethyl-4,5,6-trihydro-2-phenyl-benzo[6,7] cyclohepta[1,2-c]pyrazole (**3b**): Color: White needles. M.p.: 83 °C (benzene). IR (KBr, ν, cm^{-1}): 3055 (CH) (Aromatic), 2954 (CH) (alkyl), 1600, 1580, 1480, 1465 (C=C) (Aromatic), 1345, 1285, 1020, 746. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.92 (d, 3H, *J* = 6 Hz, CH_3), 1.35 (s, 6H, $2CH_3$), 2.33 (dd, Ha, *J* = 16.3 Hz, CH_2), 2.42 (p, 1H, *J* = 9.3 Hz, -CH), 2.64 (app.t, Hb, *J* = 16.3 Hz, CH_2), 7.11-8.25 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 16.4 (1C, -CH*CH_3*), 27.3 (2C, -C(*CH_3*)$_2$), 29.2 (1C, -CH_2-, C-4), 42.5 (1C, -*C*(CH_3)$_2$, C-6), 52.4 (1C, -*CH*CH_3, C-5), 119.2 (1C, C-3a), 120.7 (2C, Ar., C-2', C-6'), 125.2 (1C, Ar., C-7), 125.6 (1C, Ar., C-10a), 126.6 (2C, Ar., C-4', C-9), 127.2 (1C, N-C(Cl)=, C-3), 128.1 (1C, Ar., C-10), 128.9 (1C, Ar., C-8), 129.5 (2C, Ar., C-3', C-5'), 142.7 (1C, Ar., C-1'), 151.4 (1C, Ar., C-6a), 157.4 (1C, N=C-,C-10b). Anal. calcd. for $C_{21}H_{21}ClN_2$: C, 74.88; H, 6.28; N, 8.32. Found; C, 74.64; H, 6.40; N, 8.52%.

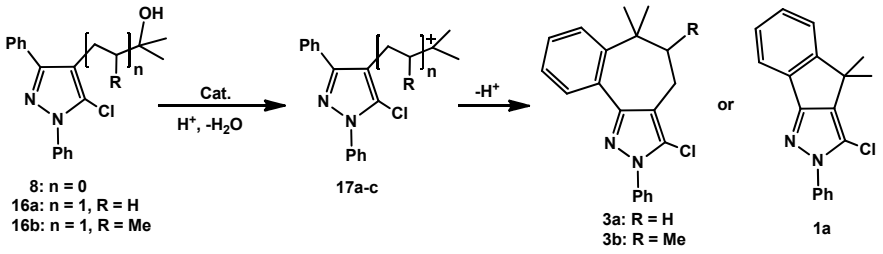
3-Chloro-2-phenylindeno[1,2-c]pyrazol-4(2H)-one (**1b**): Color: White crystals. M.p.: 144 °C (ethanol). IR (KBr, ν, cm^{-1}): 3032 (CH) (Aromatic), 2963 (CH) (alkyl), 1687 (C=O) (Ketone), 1590, 1485, 1455, 1430 (C=C) (Aromatic), 1385, 1260, 742. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.27-8.34 (9H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 109.4 (1C, C-3a), 122.6 (2C, Ar., C-2', C-6'), 126.8 (1C, Ar., C-4'), 127.4 (1C, Ar., C-8), 128.9 (1C, Ar., C-6), 129.4 (2C, Ar., C-3', C-5'), 130.6 (1C, Ar., C-5), 131.6 (1C, N-C(Cl)=, C-3), 135.8 (1C, Ar., C-7), 137.2 (1C, Ar., C-4a). 142.7 (1C, Ar., C-1'), 145.2 (1C, Ar., C-8a), 157.8 (1C, N=C-, C-8b), 197.4 (1C, C=O, C-4). Anal. calcd. for $C_{16}H_9ClN_2O$: C, 68.46; H, 3.23; N, 9.98. Found; C, 68.59; H, 3.05; N, 10.18%.

3a,4-Dihydro-2-phenyl-2H-benzo[g]indazole-3,5-dione (**2c**): Color: Yellow crystals. M.p.: 126 °C (ethanol). IR (KBr, ν, cm^{-1}): 3035 (CH) (Aromatic), 2985 (CH) (alkyl), 1693 (C=O) (ketone), 1655 (C=O) (amide), 1580, 1480, 1465 (C=C) (Aromatic), 1345, 746. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.71 (dt, 1Ha, *J* = 14.2 Hz, CH_2), 2.84 (dd, 1H, *J* = 10.4 Hz, CH), 3.11 (app. t, 1Hb, *J* = 14.2 Hz, CH_2), 7.32-8.30 (9H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 38.6 (1C, -CH_2-, C-4), 42.3 (1C, C-3a), 122.8 (2C, Ar., C-2', C-6'), 126.4 (1C, Ar., C-4'), 128.3 (1C, Ar., C-6), 129.6 (2C, Ar., C-3', C-5'), 130.4 (1C, Ar., C-9), 130.9 (1C, Ar., C-9a), 132.1 (1C, Ar., C-7), 133.5 (1C, Ar., C-8), 138.7 (1C, Ar., C-5a), 145.4 (1C, Ar., C-1'), 158.7 (1C, N=C-,C-9b), 179.4 (1C, N-C=O, C-3), 204.9 (1C, C=O, C-5). Anal. calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found; C, 73.76; H, 4.49; N, 10.22%.

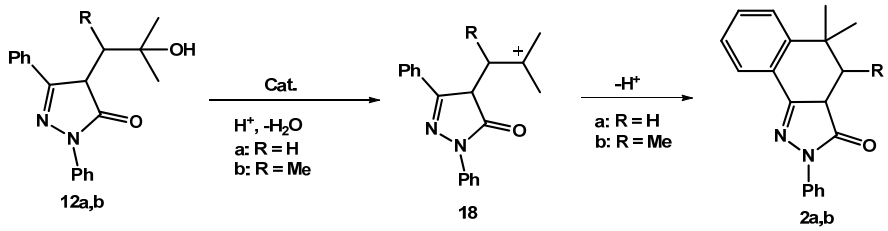
3a,4-Dihydro-4-methyl-2-phenyl-2H-benzo[g]indazole-3,5-dione (**2d**): Color: White needles. M.p.: 152 °C (ethanol). IR (KBr, ν, cm^{-1}): 3066 (CH) (Aromatic), 2964 (CH) (alkyl), 1705 (C=O) (ketone), 1663 (C=O) (amide),1597, 1575, 1480, 1444 (C=C) (Aromatic), 1385, 743. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.18 (d, 3H, *J* = 9.4 Hz, CH_3), 2.93 (d, 1H, *J* = 12.5 Hz, CH), 3.37 (p,1H, *J* = 6 Hz, CH), 7.23-8.41 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 16.5 (1C, -CH*CH_3*), 40.7 (1C, -*CH*CH_3, C-4), 46.4 (1C, C-3a), 122.6 (2C, Ar., C-2', C-6'), 126.4 (1C, Ar., C-4'), 128.5 (1C, Ar., C-6), 129.2 (2C, Ar., C-3', C-5'), 130.2 (1C, Ar., C-9), 131.3 (1C, Ar., C-9a), 132.8 (1C, Ar., C-7), 134.3 (1C, Ar., C-8), 137.7 (1C, Ar., C-5a), 144.4 (1C, Ar., C-1'), 157.7 (1C, N=C-,C-9b), 182.4 (1C, N-C=O, C-3), 207.2 (1C, C=O, C-5). Anal. calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found; C, 74.53; H, 5.07; N, 9.53%.

3-Chloro-4,5,6-trihydro-2-phenyl-benzo[6,7]cyclohepta[1,2-c]pyrazol-6-one (**3c**): Color: White needles. M.p.: 91 °C (acetone). IR (KBr, ν, cm^{-1}): 3070 (CH) (Aromatic), 2978 (CH) (alkyl), 1694 (C=O) (ketone), 1585, 1463, 1450 (C=C) (Aromatic), 1385, 1280, 1075, 745. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.62 (t, 2H, *J* = 6.2 Hz, CH_2), 2.84 (t, 2H, *J* = 6.2 Hz, CH_2), 7.19-8.30 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 13.8 (1C, -CH_2-, C-4), 52.4 (1C, -CH_2-, C-5), 119.3 (1C, C-3a), 123.2 (2C, Ar., C-2', C-6'), 126.8 (1C, Ar., C-4'), 127.4 (1C, N-C(Cl)=, C-3), 127.6 (1C, Ar., C-10), 128.2 (1C, Ar., C-8), 129.6 (1C, Ar., C-7), 130.4 (2C, Ar., C-3', C-5'), 132.7 (1C, Ar., C-10a), 135.7 (1C, Ar., C-9), 138.9 (1C, C-6a), 143.7 (1C, Ar., C-1'), 156.4 (1C, N=C-, C-10b), 208.3 (1C, C=O, C-6). Anal. calcd. for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07. Found; C, 69.79; H, 4.42; N, 9.35%.

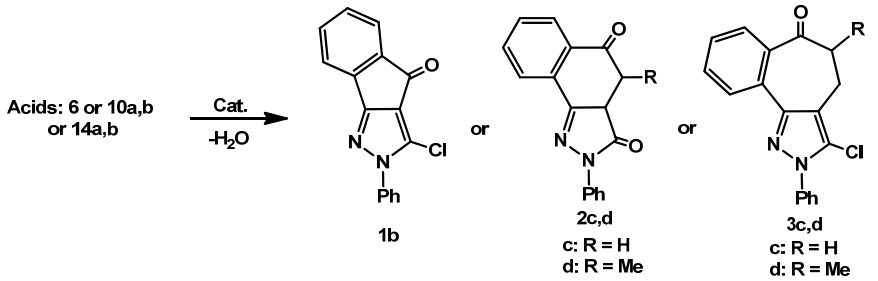
3-Chloro-4,5,6-trihydro-5-methyl-2-phenyl-benzo[6,7]cyclo hepta[1,2-c]pyrazol-6-one (**3d**): Color: White needles.



Scheme 3



Scheme 4



Scheme 5

M.p.: 164 °C (acetone). IR (KBr, ν, cm^{-1}): 3060 (CH) (Aromatic), 2965 (CH) (alkyl), 1686 (C=O) (ester), 1590, 1470, 1450 (C=C) (Aromatic), 1385, 1285, 1070, 750, 695. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.19 (d, 3H, *J* = 10.4 Hz, CH_3), 2.64 (td, Ha, *J* = 16.3 Hz, CH_2), 2.81 (p, Hb, *J* = 16.3 Hz, CH_2), 3. 42 (q, 1H, *J* = 9.3 Hz, -CH), 7.30-8.35 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 19.4 (1C, -CH*C*H$_3$), 29.5 (1C, -CH_2-, C-4), 47.2 (1C, -*C*HCH$_3$, C-5), 118.5 (1C, C-3a), 123.4 (2C, Ar., C-2', C-6'), 126.8 (1C, Ar., C-4'), 127.2 (1C, N-C(Cl)=, C-3), 128.2 (1C, Ar., C-10), 128.9 (1C, Ar., C-8), 129.2 (1C, Ar., C-7), 130.3 (2C, Ar., C-3', C-5'), 131.7 (1C, Ar., C-10a), 134.7 (1C, Ar., C-9), 138.9 (1C, Ar., C-6a), 144.5 (1C, Ar., C-1'), 157.3 (1C, N=C-, C-10b), 208.2 (1C, C=O, C-6). Anal. calcd. for $C_{19}H_{15}ClN_2O$: C, 70.70; H, 4.68; N, 8.68. Found; C, 70.92; H, 4.45; N, 8.52%.

3. Results and discussion

We first attempted to prepare the precursors heteroaryl acids required for this work (**6**, **10a**,**b** and **14a**,**b**) which are easily obtained via three different synthetic routes starting from the easily prepared 1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**4**) [56] as formulated in Scheme 1 and 2.

The first path comprised the formation of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**5**) following standard literature procedure by chloroformylation of pyrazolone **4** under Vilsmeier conditions [55]. This aldehyde was oxidized by $KMnO_4$ solution [57] to afford 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid (**6**). The second path included the conversion of substrate **4** to 4-bromo-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (**9**) following the literature procedure [58] in the presence of bromine in acetic acid. The resulting bromide **9** was allowed to react with excess of sodio-diethyl malonates [59] in ethanol followed by decarboxylation to afford substituted acetic acids **10a**,**b**.

On the other hand, the third route (path 3) involved the production of acid precursors **14a**,**b** (Scheme 2). These acids were smoothly prepared through the Perkin-type reaction [60] of aldehyde **5** with acid anhydrides and the corresponding sodium salts of acids to give substituted 3-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)acrylic acids (**11a**,**b**). The resulting acids **13a**,**b** were reduced by sodium amalgam in sodium hydroxide solution to afford **14a**,**b**.

Upon intermediate acids **6**, **10a**,**b** and **14a**,**b** are formed, they could be converted into ethyl esters **7**, **11a**,**b** and **15a**,**b** by reaction with ethanol and H_2SO_4 [61]. The resulting esters were converted to the corresponding alcohols **8**, **12a**,**b** and **16a**,**b** (Schemes 1 and 2; Table 1) by addition of two equivalents of methymagnesium iodide [62] in Et_2O/THF solution. The structures of all new alcohols were appropriately established by the usual spectroscopic methods.

The structural elucidation of alcohols **8**, **12a**,**b**, and **16a**,**b** was mainly based on IR, ^{1}H NMR, MS and elemental analyses. The IR spectra of alcohols **1a-c** showed absorption bands for a OH groups as broad bands in the range 3340-3490 cm^{-1}. The ^{1}H NMR data allowed an unambiguous statement of the heterocyclic alkanols formation. Thus, the ^{1}H NMR spectrum displayed five signals for compound **12a**. The tenth aromatic protons appear at δ 7.15-8.25 ppm.

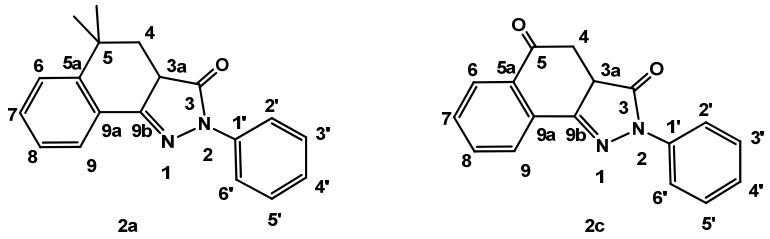


Figure 2. Diastereotopic protons embraced in pyrazolones heteropolycycles.

The aliphatic acyclic protons of the two methyls and methylene groups of the new alcohol appeared as two sets of splitting. The singlet gem-dimethyls appear at δ 1.30 ppm while doublet at δ 2.0 ppm was assigned to the up-field proton CH_2. A forth broad singlet at δ 2.55 ppm was assigned to OH. In all IR spectra of the synthesized carbinols, the characteristic peak of carbonyl groups was absent.

The cyclialkylations of alcohols **8**, **12a**,**b** and **16a**,**b** were smoothly carried out in the presence of $AlCl_3/CH_3NO_2$ or P_2O_5 or PPA catalysts under different reaction conditions gave substituted 2,4-dihydroindeno[1,2-*c*]pyrazole **1a**, 4,5-dihydro-2*H*-benzo[*g*]indazol-3(3a*H*)-ones **2a**,**b** and 4,5,6-trihydro benzo[6,7]cyclohepta[1,2-*c*]pyrazoles **3a**,**b** in good overall yields (Table 2, Scheme 3 and 4).

On the other hand, cyclialkylations of acids **6**, **10a**,**b** and **14a**,**b** were carried out in the presence of the same catalysts under varying conditions to give substituted tricyclic pyrazolones **1b**, **2c**,**d** and **3c**,**d**. The results are embedded in Table 2 and Scheme 5.

The ^{1}H NMR data allowed an unambiguous statement of the formation of heterocyclic products. The assignment of the diastereotopic protons of the methylene group directly bonded to pyrazole or pyrazolone rings (**2a**,**c** and **3b**,**d**) beside their intermediates alcohols and acids (**12a**, **16b** and **10a**, **14b**) were made on the basis of *J*-values that were obtained by direct inspection of the ^{1}H NMR spectrum which in turn showed a greatly change in chemical shifts. It is known that the extent of shielding is proportional to the electronegativity exerted by the heterocyclic ring or the neighbored functional groups and its proximity to the hydrogen [63-66].

This trend has been observed from the chemical shifts of diastereotopic hydrogens (H_a and H_b) of CH_2 group characterized by the A_2B system obtained in each series (Figure 2).

For instance, the ^{1}H NMR of tricyclic compound **2a** displayed five signals in which aromatic protons appeared at δ 6.85-8.11 ppm and the gem-dimethyls groups appeared as singlet at δ 1.40 ppm, respectively. The third quartet appeared at 2.35 ppm with coupling constant of 10.4 Hz. As expected, the remaining two signals for the diastereotopic CH_2 group exhibits a complex set of overlapped signals which were assigned to be shielded and displayed as a second order set of signals showed a triplet in average at δ 1.84 ppm with coupling constant of 14.2 Hz for one hydrogen and doublet of doublets at an average of 2.17 ppm for the other one. In comparison with the compound **2a**, the tricyclic pyrazolone **2c** showed the ^{1}H NMR chemical shifts for CH_2 protons (H_a and H_b) as a characteristic doublet of triplet for H*a* at an average of δ 2.71 ppm with a coupling constant of 14.2 Hz and a apparently triplet for H_b near δ 3.11 ppm.

4. Conclusion

In conclusion, we have developed a simple and attractive method for the synthesis of variety of new fused tricyclic pyrazoles bearing small to medium-sized alkyl residues. The synthetic approach involved Friedel-Crafts cyclialkylations of heteroaryl alkanols and acids catalyzed by $AlCl_3/CH_3NO_2$ or P_2O_5 or PPA. To the best of our knowledge, this is the first time that such novel substituted pyrazoles have been described. The results proved that Friedel-Crafts cyclialkylations can be considered as useful pathways to the syntheses of heteropolycycles.

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