European Journal of Chemistry 4 (3) (2013) 268-271

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Synthesis, characterization and antimicrobial evaluation of 1-((5,3-diaryl)-4,5-dihydro-1*H*-pyrazol-1-yl)propan-1-one

Assia Sid *, Nouara Ziani, Ouafa Demmen-Debbih, Mahieddine Mokhtari and Kaddour Lamara

Laboratory of Applied Chemistry and Materials Technology, Sciences of Material Department, Larbi Ben M'Hidi University, Oum El Bouaghi, 04000, Rue de Constantine, Algeria

**Corresponding author at: Laboratory of Applied Chemistry and Materials Technology, Sciences of Material Department, Larbi Ben M'Hidi University, Oum El Bouaghi, 04000, Rue de Constantine, Algeria.*
Tel.: +213.32421036; fax: +213.32424213. E-mail address: madamesid9@yahoo.fr (A. Sid).

ARTICLE INFORMATION

Received: 08 May 2013
Received in revised form: 07 June 2013
Accepted: 09 June 2013
Online: 30 September 2013

KEYWORDS

Pyrazoles
Chalcones
Propanoic acid
Hydrazine hydrate
Antimicrobial activity
1,3-Dipolar cycloaddition

ABSTRACT

1-((5,3-Diaryl)-4,5-dihydro-1*H*-pyrazol-1-yl)propan-1-one, 6-10, have been synthesized by the reaction of chalcone derivatives, **1-5**, with hydrazine hydrate in hot propanoic acid solution. All these compounds were characterized by different spectroscopic techniques (FT-IR, ^{1}H and ^{13}C NMR) and elemental analyses. All the synthesized products were evaluated for antimicrobial activity. All the compounds exhibited significant to moderate antimicrobial activity.

1. Introduction

Heterocyclic compounds have so far been synthesized mainly due to the wide range of biological activities. Much attention has been paid to the synthesis of heterocyclic compounds bearing nitrogen containing ring system, like pyrazoles mainly due to their higher pharmacological activity. Over the years, the chemistry of 1*H*-pyrazoles has received considerable attention [1,2]. It is worthy of note that substances containing a 1*H*-pyrazole moiety have been described as having potential therapeutic utility, such as anti-inflammatory [3-5], antidepressant [6,7], antipyretic [8], antibacterial [9-14], antifungal [12,15] and antitumoral [16]. Of particular interest is the use of 1*H*-pyrazoles as synthetic intermediates for preparing cyclopropane [17-19] and pyrazole derivatives [1,20-26]. 1H-Pyrazoles have usually been prepared by starting from aldehydes or ketones, which have either actual or potential α,β-unsaturation [1,27-41]. 1,3-Dipolar cyclo-additions between diazoalcanes and different types of molecules containing activated double bonds are also exploitable reactions [1,16,17,42,43].

In our case, substituted chalcones, **1-5**, were prepared by the reaction of benzaldehyde derivatives with acetophenone derivatives in the presence of aqueous solution of sodium hydroxide and ethanol by the Claisen-Schmidt condensation method to afford corresponding 1-((5,3-diaryl)-4,5-dihydro-1*H*-pyrazol-1-yl)propan-1-one, **6-10**, by their 1,3-dipolar cycloaddition to hydrazine hydrate in hot propanoic acid solution.

2. Experimental

2.1. Instrumentation

Melting points were determined with (Bransted/-Electrothermal) apparatus and are uncorrected. IR spectra were recorded for KBr pellets on a Perkin-Elmer FT-IR-01 spectrophotometer. 1H and 13C NMR spectra are recorded on a Bruker spectrometer respectively at 400 and at 100 MHz in $CDCl_3$ (internal standard TMS, δ = 0.0 ppm) at room temperature. TLC were performed on Kieslgel 60 F_{254} (Merck) layer using toluene: ethyl acetate (3:2, *v:v*) as eluents. Elemental analyses were performed on Perkin-Elmer 240B micro analyser, and the analytical results were within ±0.4% of the theoretical values.

2.2. Synthesis

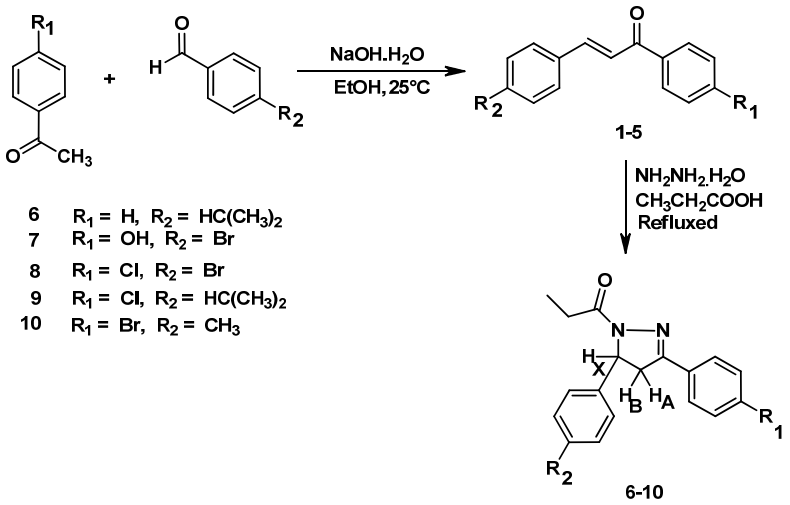
2.2.1. Synthesis of chalcones (1-5)

A mixture of substituted acetophenones (0.01 mole) and substituted benzaldehydes (0.01 mole) was stirred in ethanol (50 mL) and then a solution of 15 mL sodium hydroxide (0.04 mole) was added. The mixture was kept for four hours at room temperature and then it was poured into crushed ice and acidified with diluted HCl. The chalcones derivative precipitates out as solid. Then it was filtered and crystallized from ethyl acetate (Scheme 1) [44].

2.2.2. Synthesis of 1-((5,3-diaryl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one, 6-10

A mixture of chalcone derivatives (**1-5**, 10 mmoles), hydrazine hydrate (50 mmoles) and propanoic acid (40 mL) was refluxed for 12 hours then poured into crushed ice. The precipate was separated by filtration, washed free of acid and crystallized from ethanol to afford 1-((5,3-diaryl)-4,5-dihydro-1*H*-pyrazol-1-yl)propan-1-one, **6-10** (Scheme 1).

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online) © 2013 EURJCHEM
DOI:10.5155/eurjchem.4.3.268-271.824



Scheme 1

1-(5-(4-Isopropylphenyl)-3-(4-phenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**6**): Color: Pal crystal. Yield: 70%. M.p.: 140-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.12 (3H, t, CH_3), 1.23 (6H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 2.54 (2H, q, CH_2), 2.90 (1H, sept, *J* = 6.9 Hz, $CH(CH_3)_2$), 3.32 (1H, dd, *J*= 4.6, 17.7 Hz, H_A), 3.82 (1H, dd, *J* = 11.8, 17.7 Hz, H_B), 5.52 (1H, dd, *J* = 4.6, 17.7 Hz, H_X), 7.78-7.69 (2H m, H Ar), 7.48-7.38 (3H, m, H Ar), 7.22-7.14 (4H, m, H Ar). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 15.12, 23.90, 23.92, 33.77, 40.52, 42.60, 58.80, 125.62, 126.69, 127.08, 128.81, 130.62, 130.97, 137.94, 148.59, 160.10. Anal. calcd. for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.69; H, 7.52; N, 8.70%.

1-(5-(4-Bromophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**7**): Color: Pal crystal. Yield: 80%. M.p.: 148-149 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.16 (3H, t, CH_3), 2.52 (2H, q, CH_2), 3.28 (1H, dd, *J* = 18.4, 4.8 Hz, H_A), 3.85 (1H, dd, *J* = 18.4, 11.9 Hz, H_B), 5.54 (1H, dd, *J* = 11.9, 4.8, 1.0 Hz, H_X), 7.44-7.41 (2H, m, H Ar), 7.29-7.27 (2 H, m, H Ar), 7.18-7.14 (4H, m, H Ar), 10.08 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 15.14, 40.55, 41.98, 58.89; 125.71, 126.75, 127.25, 128.91, 131.42, 131.72, 139.14, 148.09, 155.25, 160.10. Anal. calcd. for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.50. Found: C, 57.47; H, 4.52; N, 7.46%.

1-(5-(4-Bromophenyl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**8**): Color: Pal yellow crystal. Yield: 87%. M.p.: 144-145 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.14 (3H, t, CH_3), 2.53 (2H, q, CH_2), 3.27 (1H, dd, *J* = 18.3, 4.8 Hz, H_A), 3.82 (1H, dd, *J* = 18.3, 11.8 Hz, H_B), 5.53 (1H, dd, *J* = 11.8, 4.8, 1.0 Hz, H_X), 7.45-7.30 (4H, m, H Ar), 7.25-7.20 (4H, m, H Ar). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 15.17, 40.57, 42.40, 57.70, 125.60, 126.59, 127.02, 128.80, 130.59, 130.95, 137.86, 148.48, 155.83, 160.15. Anal. calcd. for $C_{18}H_{16}BrClN_2O$: C, 55.19; H, 4.11; N, 7.15, Found: C, 55.12; H, 4.07; N, 7.11%.

1-(5-(4-Isopropylphenyl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**9**): Colar: Pal crystal. Yield: 76%. M.p.: 142-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.18 (3H, t, CH_3), 1.25 (6H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 2.92 (1H, sept, *J*= 6.9 Hz, $CH(CH_3)_2$), 2.58 (2H, q, CH_2), 3.29 (1H, dd, *J* = 18.4, 4.8 Hz, H_A), 3.81 (1H, dd, *J* = 18.4, 11.9 Hz, H_B), 5.51 (1H, dd, *J* = 11.9, 4.8, 1.0 Hz, H_X), 7.44-7.27 (4H, m, H Ar), 7.18-7.14 (4H, m, H Ar). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 15.13, 23.91, 23.93, 33.79, 40.56, 41.95, 58.79, 125.61, 126.65, 127.05, 128.81, 130.62, 130.97, 138.94, 147.69, 154.75, 159.30. Anal. calcd. for $C_{21}H_{23}ClN_2O$: C, 71.07; H, 6.53; N, 7.89. Found: C, 71.04; H, 6.49; N, 7.85%.

1-(5-(4-Methylphenyl)-3-(4-bromophenyl)-4,5-dihydro-1H-pyrazol-1-yl)propan-1-one (**10**): Color: Pal crystal. Yield: 78%. M.p.: 145-144 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.15 (3H, t, CH_3), 1.20 (3H, s, CH_3), 2.55 (2H, q, CH_2), 3.27 (1H, dd, *J* = 17.7, 4.8 Hz, H_A), 3.75 (1H, dd, *J* = 17.7, 11.7 Hz, H_B), 5.50 (1H, dd, *J* = 11.7, 4.8, 1.0 Hz, H_X), 7.77-7.57 (4H, m, H Ar), 7.42-7.35 (4H, m, H Ar). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 15.10, 23.86, 40.55, 42.58, 58.79, 125.62, 126.69, 126.90, 128.73, 130.60, 130.85, 137.35, 148.32, 155.55, 160.30. Anal. calcd. for $C_{19}H_{19}BrN_2O$: C, 61.46; H, 5.15; N, 7.54. Found: C, 61.42; H, 5.10; N 7.52%.

2.3. Antimicrobial activity

The synthesized compounds **6-10** were screened *in vitro* for antibacterial activity against *Escherchia coli, Salmonella typhi, Staphylococcus aureus and Bacillus subtilis* at the concentrations 200, 300, 400 and 500 µg/mL and for antifungal activity against *Aspergillus niger* at 100, 200, 300, 400 µg/mL by cup-plate agar diffusion method [45]. The concentrations used in screening were chosen after determining the MICs of each compound. The solvent used was dimethylsulfoxide (DMSO) further diluted with water. Muller Hinton agar was used as the growth medium for the bacterial species and Sabouraud's agar was the growth medium for the fungal species. DMSO was used as a control for all the type of microorganisms. The control showed no activity against the strains of microorganisms used. The results presented in Table 1 and 2 are obtained after 48 hours of incubation at 35 °C for antibacterial test and at 28-30 °C for antifungal test. They are compared with standard drugs penicillin for antibacterial activity and Greseofulvin for antifungal activity by measuring the zone of inhibition in mm.

3. Results and discussion

Compounds **1-5** were treated with commercial hydrazine hydrate in propanoic acid under reflux. The progress of these reactions could be easily monitored by TLC showing a complete transformation of starting materials to single products, which were easily isolated by cooling at <0 °C and filtration of the precipitated solid. Highly pure products were isolated in this manner and were crystallized from ethanol. They were identified by IR and high field NMR spectroscopy as 1-((5,3-diaryl)-4,5-dihydro-1*H*-pyrazol-1-yl)propan-1-one, **6-10**.

Table 1. Antibacterial screening results of the compounds **6**-**10**.

Compound	*Escherchia* Coli	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus subtilis*
6	09	11	14	12
7	14	18	26	17
8	15	20	28	19
9	11	14	23	13
10	10	11	19	25
Penicillin	18	25	40	17
DMSO	-	-	-	-

-No antibacterial activity

Table 2. Antifungal screening results of the compounds **6**-**10**.

Compound	*Aspergillus niger*	*Aspergillus flavus*	*Pencillium chrysogenum*	*Fusirium moneliforme*
6	-	+	+	+
7	-	-	+	+
8	-	-	-	-
9	+	+	-	+
10	-	+	+	+
Greseofulvin	-	-	-	-
Control	+	+	+	+

- No Growth: Antifungal activity; + Growth: No antifungal activity.

The IR spectrum of these compounds exhibited bands due to: C=O of propanoyl group at 1680 cm^{-1}, C=N of pyrazoline ring at 1650 cm^{-1}, C=C at 1590 cm^{-1} and C-N at 1150 cm^{-1}. Furthermore, their ^1H NMR spectra in $CDCl_3$ displayed the ethyl signals of the propanoyl group at 1.12-1.18 ppm (triplet of CH_3) and at 2.52-2.58 ppm (quadruplet of CH_2) as well as the characteristic ABX three-spin system of the neighboring methylene and methyne protons of the pyrazoline ring: 5.50-5.54 ppm (dd, H_X), 3.85-3.75 ppm (dd, H_B) and 3.27-3.32 ppm (dd, H_A). The ^{13}C NMR spectra of all the compounds **6**-**10** corroborated the 1*H*-pyrazole structure with the signals of carbon atoms C-3 (154-156 ppm), C-4 (41-43 ppm) and C-5 (57-59 ppm) as well as the presence of *N*-propanoyl group.

The investigation of antibacterial screening results indicates that compounds **7** and **8** show promising activity and compounds **6** and **10** poor activity against *Escherchia coli*. Compounds **7** and **8** show good activity against *Salmonella typhi*. Compounds **7**, **8** and **9** show high activity and compound **6** shows low activity against *Staphylococcus areus*. Compounds **6**, **7**, **8**, **10** show inhibitory effect against *spergillus niger* and compounds **7** and **8** show inhibitory effects against *spergillus flavus*. Compounds **8**, **9** show inhibitory effects against *Penicillium chrysogenum*, similar compound **8** shows inhibitory effect against *Fusirium moneliforme*. Remaining compounds are inactive against all the fingers.

4. Conclusion

In conclusion, the synthesized 1*H*-pyrazoles having pharmacophores such as chloro, bromo groups are present in one moiety exhibited best antimicrobial activity. The data reported in this article may be helpful guide for the medicinal chemist who is working in this area.

Acknowledgements

We thank Professor Mustapha Bouhenguel director of Laboratory of Applied Chemistry and Materials Technology of the University of Oum El Bouaghi for his support of this work. We gratefully acknowledge Mr. Paul Mosset Doctor at the University of Rennes 1. France for providing spectroscopic analysis and the director of the Microbiology Laboratory of the Hospital of Mohamed Boudiaf of Oum El Bouaghi. Algeria for his support of the biological section.

References

[1]. Berhr, L. C.; Fusco, F.; Jarboe, C. H. The Chemistry of Heterocyclic Compounds, edition, Wiley-Interscience, 1967.
[2]. Elguero, J. In Comprehensive Heterocyclic Chemistry, edition, Pergamon: Oxford, 1984.
[3]. Bansal, E.; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2001**, *36*, 81-91.
[4]. Kumar, A.; Archana; Sharma, S.; Malik, N.; Sharma, P.; Kaushik, K.; Saxena, K. *Indian J. Chem. B* **2004**, *43*, 1532-1536.
[5]. Barsoum, F. F.; Hosni, H. M.; Girgis, A. S. *Bioorg. Med. Chem.* **2006**, *14*, 3929-3937.
[6]. Palaska, E.; Aytemir, M.; Uzbay, I. T.; Erol, D. *Eur. J. Med. Chem.* **2001**, *36*, 539-543
[7]. Prasad, Y. R.; Rao, A. L.; Prasoona, L.; Murali, K.; Kumar, P. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5030-5034.
[8]. Souza, F. R.; Souza, V. T.; Ratzlaff, V.; Borges, L. P.; Oliveira, M. R.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P.; Mello, C. F. *Eur. J. Pharmacol* **2002**, *451*, 141-147.
[9]. Mamolo, M. G.; Zampieri, D.; Falagiani, V.; Viol, L.; Banafi, E. *II Farmaco* **2001**, *56*, 593-599.
[10]. Patel, P.; Koregaokar, S.; Shah, M.; Parekh, H. *Farmaco* **1996**, *51*, 59-63.
[11]. Grant, N.; Mishriky, N.; Asaad, F. M.; Fawzy, N. G. *Pharmazie* **1998**, *53*, 543-547.
[12]. Nauduri, D.; Reddy, G. B. S. *Chem. Pharm. Bull.* **1998**, *46*, 1254-1260.
[13]. Holla, B. S.; Akberali, P. M.; Shivananda, M. K. *II Farmaco* **2000**, *55*, 256-263.
[14]. Solankee, A.; Thakor, I. *Indian J. Chem. B* **2006**, *45*, 517-522.
[15]. Tiwari, N.; Dwivedi, B.; Nizamuddin, N. Boll. *Chim. Farm.* **1989**, *128*, 332- 335.
[16]. Nimavat, K. S.; Popat, K. H.; Joshi, H. S. *Indian J. Heterocycl. Chem* **2003**, *12*, 225-228.
[17]. Van Auken, T. V.; Rinehart, K. L. Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3736-3743.
[18]. Mc Greer, D. E.; Morris, P.; Carmichael, G. *Can. J. Chem.* **1963**, *41*, 726-731.
[19]. Fieser, M.; Fieser, L. F. Reagents for Organic Synthesis, edition, Wiley-Interscience, 1969.
[20]. Freeman, J. P. *J. Org. Chem* **1964**, *29*, 1379-1382.
[21]. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955-3957.
[22]. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis* **2004**, 1015-1020.
[23]. Zolfigol, M. A.; Azarifar, D.; Mallakpour, S.; Mohammadpoor-Baltork, I.; Forghaniha, A; Maleki B; Abdollahi-Alibeik, M. *Tetrahedron Lett.* **2006**, *47*, 833-836.
[24]. Lokhand, P.; Hasanzadeh, K.; Konda, S. G. *Eur. J. Chem.* **2011**, *2*, 223-228.
[25]. Abdelhamid, A. O.; Fahmi, A. A.; Noury, K.; Halim, M. *Eur. J. Chem.* **2011**, *2*, 317-223.
[26]. Abdelhamid, A. O.; Fahmi, A. A.; Ali Mohamed Alscheflo, A. *Eur. J. Chem.* **2012**, *3*, 129-137.
[27]. Levai, A. *J. Heterocycl. Chem.* **2002**, *39*, 1-13.
[28]. Blicke, F. F.; Burkhalter, J. H. *J. Am. Chem. Soc.* **1942**, *64*, 451-454.
[29]. Beech, S. G.; Turnbull, J. H.; Wilson, W. *J. Chem. Soc. Chem. Commun.* **1952**, 4686-4690.
[30]. Petersen, R. J.; Skell, P. S. Organic Synthesis Collective, edition, John Wiley, 1973.
[31]. Smith, L. I.; Rogier, E. R. *J. Am. Chem. Soc.* **1951**, *73*, 3840-3849.
[32]. Mehr, L.; Becker, E. I.; Spoerri, P. E. *J. Am. Chem. Soc.* **1955**, 77, 984-989.
[33]. Fieser, M.; Fieser, L. F. Reagents for Organic Synthesis, edition, Wiley-Interscience, 1969.
[34]. Hanson, G. A. *Bull. Soc. Chim. Belg.* **1958**, *67*, 707-711.

[35]. Huang, Y. R.; Katzenellenbogen, *J. A. Org. Lett* .**2000**, *2*, 2833-2836.
[36]. Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V. *J. Org. Chem.* **2001**, *66*, 6787-6791.
[37]. Kolhe, S. V.; Doshi, A. G.; Raut, A. W. *Indian J. Heterocycl. Chem.* **2003**, *12*, 281-283.
[38]. Kidwai, M.; Kukreja, S.; Thakur, R. *Lett. Org. Chem.* **2006**, *3*, 135-139.
[39]. Lévai, A.; Jeko, J. *J. Heterocycl. Chem.* **2006**, *43*, 111-115.
[40]. Siddiqui, A. H.; Satyanarayana, Y.; Srinivas, M.; Rajeshwar, K. *J. Indian Chem. Soc*. **1992**, *69*, 846-848.
[41]. Agrawal, N. N.; Soni, P. A. *Indian J. Chem. B* **2007**, *43*, 532-534.
[42]. Reimlinger, H.; Moussebois, C. *Chem. Ber.* **1965**, *98*, 1805-1813.
[43]. Garcia Ruano, J. L.; Alonso de Diego, S. A.; Blanco, D.; Martin Castro, A. M.; Martin, M. R.; Rodriguez Ramos, J. H. *Org. Lett.* **2001**, *3*, 3173-3176.
[44]. Sid, A.; Lamara, K.; Mokhtari, M.; Ziani, N.; Mosset, P. *Eur. J. Chem.* **2011**, *2*, 311-313.
[45]. Barry, A L.; Antimicrobial susceptibility test, Principle and practice, (Illus Lea and Fehniger, Philedelphia, USA) 1976.