European Journal of Chemistry 3 (2) (2012) 179-185

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Tetra-*n*-butylammonium fluoride-mediated dimerization of (α-methylbenzylidene)malononitriles to form polyfunctional 5,6-dihydropyridines derivatives under solvent-free conditions

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ARTICLE INFORMATION

Received: 25 November 2011
Received in revised form: 09 January 2012
Accepted: 09 January 2012
Online: 30 June 2012

KEYWORDS

Dimerization
X-ray crystallography
Solvent-free conditions
Alkylidenemalononitrile
Acetophenone derivatives
Knoevenagel condensation

ABSTRACT

A series of polyfunctional dihydropyridine **28**-**46** were prepared *via* dimerization of readily available substituted (α-methylbenzylidene)-malononitriles **10**-**27** by treating with neat TBAF.3H$_2$O under solvent-free conditions at 85-90 °C. All the dimers **28**-**46** were obtained in high yield from their corresponding substituted alkylidenemalononitriles except in the case of 2-chloro (**15**), 2-hydroxy (**21**), and 2-nitro (**26**) substituted alkylidenemalononitriles where the reaction was unsuccessful due to the steric interaction between methylene group and the substituents present at *ortho* position. The X-ray crystallographic studies of compounds **28** and **30** were carried out to confirm the structure of dimerized product. The method is eco-friendly and wider is scope to prepare a range of substituted dihydropyridine derivatives **28**-**46**.

1. Introduction

Alkylidenemalononitriles are important class of compounds in organic chemistry. They are derived from acetophenone derivatives *via* Knoevenagel condensation [1-3] and frequently used in the preparation of many medicinally important heterocyclic compounds. Pyridine ring containing compounds are also important class of the heterocyclic compounds, which are frequently used in the many fields including medicinal chemistry, agro chemicals etc. [4]. Pyridine ring is the basic unit in many known natural products and medicinally important compounds [5]. For example, nifedipine **1** and its different derivatives[4] contains pyridine core ring in their structure (Figure 1). These compounds show significant biological potential against cardiovascular diseases (calcium antagonist) [5,6]. Many research groups are involved in the synthesis of useful pyridine derivatives possessing significant biological potential. Our group is also interested in the synthesis of potentially useful pyridine derivatives *via* efficient, cost-effective and scalable methods. It is envisaged that preparation of polyfunctional 5,6-pyridine derivatives *i.e.* compound **2** would carry significant biological interests (Figure 1).

Towards our interest, readily available alkylidenemalononitriles **10**-**27** were selected as suitable candidates due to the reactive nature of the dicyanoolefin and the acidic nature of the methyl group. Both of these functionalities are very advantageous in promoting the dimerization reaction to prepare desired 5,6-dihydropyridine derivatives **28**-**46** (Scheme 1). Previously, Dunkel and Heb (1997) [7] reported the synthesis of different dicyano substituted dimers in the presence of DIMCARB (dimethylamine carbondioxide complex), whilst Abdelrazak *et al.* (2011) [8] carried out the dimerization of phenyl alkylidenemalononitrile in ethanol by using excessive amount of NaOEt to complete the reaction. However, we have developed a novel solvent-free method, where reaction is mediated by TBAF.3H$_2$O (Tetrabutylammonium fluoride trihydrate) to produce highly functionalized compound **8**. These conditions are eco-friendly, wider in scope and free of anhydrous environment. We have explored this method on a range of different substituted alkylidenemalononitriles **10**-**27** and synthesized different dihydropyridine derivatives **28**-**46**.

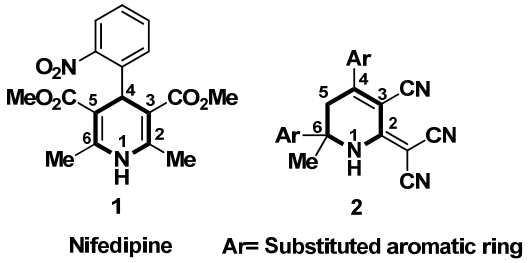
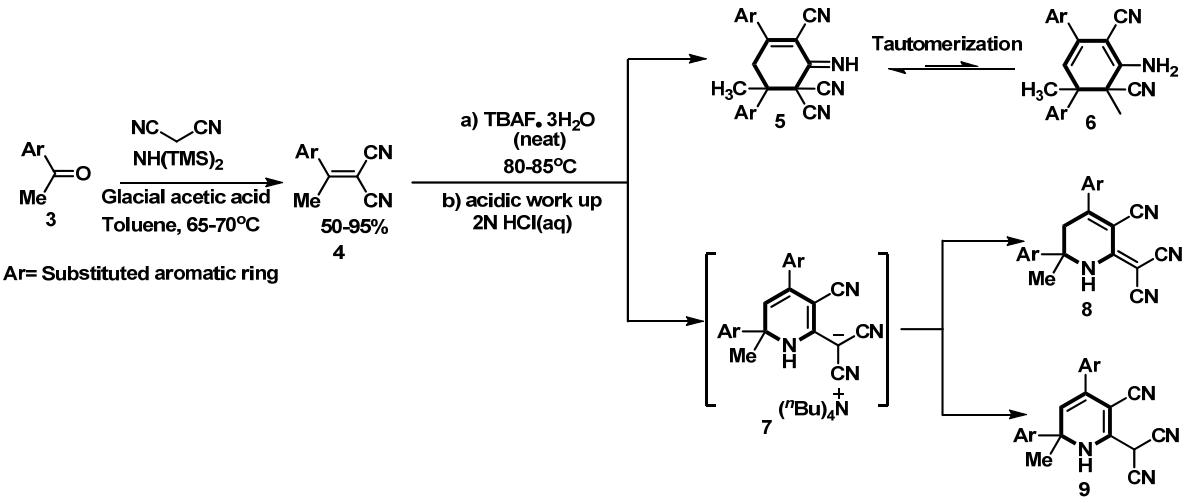


Figure 1. Nifedipine and related polyfunctional pyridine derivatives.

TBAF (Tetrabutylammonium fluoride) is commonly used as desylating agent in organic reactions [9]. However, in last few years chemists have explored many utilities of this reagent which involves nucleophilic substitution to synthesize organo-fluoro compounds [10], cyclization reactions to produce different heterocyclic rings systems *via* 5-*exo-dig* cyclization or 6-*endo-dig* cyclization [11-13], oxidation of aromatic aldehydes to benzoic acid [14] [3+2]-cycloaddition (click chemistry) [15] and [4+2]-cycloaddition [16].

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.3.2.179-185.562



Scheme 1

Homoallyl coupling of aryl halides [17], activation of epoxide ring opening with aryl sulfonamide to form morpholine derivatives [18] and *N*-arylation of benzazoles [19] are some other applications of TBAF in organic chemistry. Thus, we explored TBAF.$3H_2O$ as a base for the dimerization of alkylidenemalononitriles **10**-**27** under solvent-free conditions.

2. Experimental

All the acetophenone derivatives and other starting materials were used without purification unless otherwise stated. Infrared spectra were recorded on Shimadzu FTIR 8900 spectrometer and ^{1}H NMR spectra were obtained on Bruker 300 MHz and 400 MHz spectrometers. Coupling constant were calculated in Hertz (Hz). Mass spectra were obtained at JEOL MS Route 600 H spectrometer by using electron impact (EI+) techniques. HRMS was carried out at Thermo Finnigan MAT 95XP instrument. Single crystal X-ray diffraction data was collected on Bruker Smart APEX II, CCD 4-K area detector diffractometer. Data reductions were performed by using SAINT program and refined by full-matrix least squares on F^2 by using the SHELXTL-PC package [20]. The figures were plotted with the aid of ORTEP program [21]. The Merck silica gel 60 was used for column chromatography.

2.1. General procedure for the synthesis of polyfunctional 5,6-dihydropyridine derivatives (28-46)

In a typical reaction, an oven dried screw-capped vial having magnetic stirrer bar was charged with alkylidene-malononitrile (**10**-**27**) (1.0 equiv) and neat TBAF.$3H_2O$ (1.0 equiv). The reaction mixture was then heated at 85-90 °C with constant stirring for 15 h. The completion of the reaction was monitored by Thin layer chromatography (TLC) analysis. The reaction mixture was cooled to room temperature and diluted with dioxane (2-3 mL) and then 1.0 M HCl (100 mL) aqueous solution to remove excess TBAF. The resulting mixture was stirred for additional 5 min and then formed precipitate was filtered and washed with more 1.0 M HCl to give the pure compounds **28**-**46** in good to excellent yield (52 to 95%). The structure of these compounds **28**-**46** was confirmed by using different spectroscopic techniques including ^{1}H NMR, ^{13}C NMR, EI-HRMS and IR spectroscopy.

2-(3-Cyano-6-methyl-4,6-diphenyl-5,6-dihydropyridin-2(1H)-ylidene)malono-nitrile (**28**): Brown solid. Yield: 98%. M.p.: 193-195 °C [Lit. [7]: 201-203 °C). IR (KBr, ν_{max}, cm^{-1}): 3448 (NH), 2925, 2215, 1598, 1546, 1445, 1257. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.50-7.40 (6H, m, ArH), 7.35 (2H app d, *J* = 8.0 Hz, ArH), 7.24 (2H app d, *J* = 8.0 Hz, ArH), 6.58 (1H, brs, NH), 3.49 (1H, d, *J* = 18.0 Hz, CH_2), 3.15 (1H, d, *J* = 18.0 Hz, CH_2), 1.79 (3H. s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.5, 157.2, 141.3, 135.5, 132.3, 129.5, 129.2, 128.6, 127.9, 124.4, 114.6, 112.7, 112.6, 102.0, 56.8, 54.2, 45.7, 29.3. HRMS calcd. for $C_{22}H_{16}N_4$ (M): 336.1375, Found: 336.1355. The data are identical to those previously reported [8]. X-ray crystallographic data : $C_{22}H_{16}N_4$, (Mr = 336.39 g/mol), Monoclinic, space group *P*21/c, *a* = 6.4827(6) Å, *b* = 16.2837(16) Å, *c* = 17.8649(17) Å, *α* = 90°, *β* = 100.047(2)°, *V* = 1856.9(3)Å ^{3}, *Z* = 4, ρ_{calc} = 1.203 mg/m^3, *F*(000) = 704, *μ*(MoKα) = 0.71073 Å, max/min transmission: 0.9891/0.9656, crystal dimensions: 0.48 x 0.19 x 0.15, 1.70° < θ< 25.5° , 10830 reflections were collected, of which 3442 reflections were observed (R_{int} = 0.0248). The *R* values were: R1 = 0.0433, wR2 = 0.1043 for I > 2σ(I), and R1 = 0.0634, wR2 = 0.1182 for all data; max/min residual electron density: 0.123/-0.136 e Å^{-3}.

2-(3-Cyano-6-methyl-4,6-dip-tolyl-5,6-dihydropyridin-2(1H)-ylidene)malono-nitrile (**29**): Light brown solid. Yield: 95%. M.p.: 125-128 °C. IR (KBr, ν_{max}, cm^{-1}): 3391 (NH), 3279, 2923, 2214, 1591, 1427, 1259. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.32 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.25-7.18 (4H, m, Ar*H*), 6.11 (2H, d, *J* = 8.0 Hz, Ar*H*), 6.50 (1H, br s, NH), 3.46 (1H, d, *J* = 18, CH_2), 3.09 (1H, d, *J* = 18, CH_2), 2.37 (3H, s, CH_3), 2.33 (3H, s, CH_3), 1.76 (3H. s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 166.8, 157.8, 143.4, 138.4, 132.6, 130.0, 129.8, 128.2, 124.4, 114.9, 113.3, 113.1, 100.9, 56.7, 53.2, 45.4, 29.3, 21.6, 20.9. HRMS calcd. for $C_{24}H_{20}N_4$ (M): 364.1688, Found: 364.1645.

2-(3-Cyano-4,6-bis(4-fluorophenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**30**): Dark brown solid. Yield: 75%. M.p.: 120-122 °C. IR (KBr, ν_{max}, cm^{-1}): 3446 (NH), 2216, 1602, 1507, 1432, 1237. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.39 (2H, app dd, *J* = 8.8 Hz, 5.0 Hz, Ar*H*), 7.23 (2H, app dd, *J* = 9.0 Hz, 5.0 Hz, Ar*H*), 7.12 (4H, app dd, *J* = 16 Hz, 8.5 Hz, Ar*H*), 6.41 (1H, br s, NH), 3.40 (1H, d, *J* = 18 Hz, CH_2), 3.15 (1H, d, *J* = 18 Hz, CH_2), 1.79 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.2, 164.9, 163.7, 163.7, 161.3, 157.1, 133.2, 137.1, 130.5, 130.4, 126.4, 126.3, 116.8, 116.6, 116.6, 116.4, 114.5, 112.6, 112.5, 101.9, 56.5, 52.3, 45.7, 29.3. HRMS calcd. for $C_{24}H_{14}F_2N_4$ (M): 372.1187, Found: 372.1166. X-ray crystallographic data: Yellow crystals, $C_{22}H_{14}F_2N_4$ (Mr = 372.37 g/mol), triclinic, space group *P*-1, *a* = 6.7445(8) Å, *b* = 9.5052(12) Å, *c* = 14.6186(18) Å, α = 88.777°, *β* = 78.218(2)°, *γ* = 80.893(2)°, *V* = 905.80(19) Å^3, *Z* = 2, ρ_{calc} = 1.365 mg/m^3, *F*(000) = 384, *μ*(MoKα) = 0.71073 Å, max/min transmission: 0.9836/0.9518, crystal dimensions: 0.51 x 0.31 x 0.17, 1.42°<

θ< 25.5 °, 10262 reflections were collected, of which 3372 reflections were observed (R_{int} = 0.0162). The *R* values were: R1 = 0.0380, wR2 = 0.0979 for I > 2σ(I), and R1 = 0.0434, wR2 = 0.1031 for all data; max/min residual electron density: 0.221/-0.223 e Å^{-3}.

2-(3-Cyano-4,6-bis(3-fluorophenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**31**): Yellow solid. Yield: 75%. M.p.: 130-135 °C. IR (KBr, ν_{max}, cm^{-1}): 3249 (NH), 2222, 2204, 1614, 1584, 1487, 1437, 1270. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.45-7.39 (2H, m, Ar*H*), 7.22-7.15 (2H, m, Ar*H*), 7.07 (1H, app td, *J* = 8.0 Hz, 2.0 Hz, Ar*H*), 7.03-6.99 (2H, m, Ar*H*), 6.94 (1H, app dt, 7.6, 2.0, Ar*H*), 6.15 (1H, br s, NH), 3.40 (1H, d, *J* = 18 Hz, CH_2), 3.16 (1H, d, *J* = 18 Hz, CH_2), 1.79 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 164.5, 164.1, 163.9, 162.0, 161.4, 156.4, 144.0, 143.9, 137.4, 137.3, 131.4, 131.4, 131.3, 131.2, 123.7, 123.6, 120.1, 120.0, 119.4, 119.2, 116.1, 115.9, 114.9, 114.7, 114.2, 112.1, 112.0, 111.9, 111.8, 103.0, 56.6, 56.5, 55.6, 45.5. HRMS calcd. for $C_{24}H_{14}F_2N_4$ (M): 372.1187, Found: 372.1176.

2-(3-Cyano-4,6-bis(4-chlorophenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**32**): Brown solid. Yield: 90%. M.p.: 132-135 °C. IR (KBr, ν_{max}, cm^{-1}): 3449 (NH), 2218, 1593, 1542, 1489, 1260. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.42 (4H, app t, *J* = 8.8 Hz, Ar*H*), 7.22 (2H, d, *J*= 8.7 Hz, Ar*H*), 7.16 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.43 (1H, br s, NH), 3.39 (1H, d, *J* = 18 Hz, CH_2), 3.15 (1H, d, *J* = 18 Hz, CH_2), 1.78 (3H. s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 164.9, 156.9, 139.9, 138.8, 134.7, 133.7, 129.6, 129.6, 129.3, 125.9, 114.5, 112.6, 112.6, 102.2, 56.6, 54.4, 45.3, 29.3. HRMS calcd. for $C_{22}H_{14}Cl_2N_4$ (M): 404.0596, Found: 404.0571.

2-(3-Cyano-4,6-bis(4-bromophenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**34**): Dark brown solid. Yield: 90%. M.p.: 138-140 °C. IR (KBr, ν_{max}, cm^{-1}): 3438 (NH), 1591, 1544, 1429, 1259. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.56 (4H, app dd, *J* = 16 Hz, 8.4 Hz, Ar*H*), 7.21 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.09 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.83 (1H, br s, NH), 3.38 (1H, d, *J* = 18 Hz, CH_2), 3.15 (1H, d, *J* = 18 Hz, CH_2), 1.77 (3H, s, CH_3): ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 167.3, 157.2, 142.3, 134.4, 132.0, 132.5, 130.2, 127.3, 125.9, 120.8, 115.3, 114.6, 113.4, 101.4, 56.7, 50.0, 43.5, 28.0. HRMS calcd. for $C_{22}H_{15}Br_2N_4$ (M+H): 492.9663, Found: 492.9691.

2-(3-Cyano-4,6-bis(3-bromophenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**35**): Yellow solid. Yield: 84%. M.p.: 148-150 °C. IR (KBr, ν_{max}, cm^{-1}): 3447 (NH), 3285, 2220, 2190, 1585, 1560, 1433, 1408. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.63 (1H, app dt, *J* = 6.4 Hz, 1.6 Hz, Ar*H*), 7.51 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.40 (2H, app d, *J* = 6.4 Hz, Ar*H*), 7.34-7.30 (H, m, Ar*H*), 7.16 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.15 (1H, br s, NH), 3.39 (1H, d, *J* = 18 Hz, CH_2), 3.14 (1H, d, *J* = 18 Hz, CH_2), 1.79 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 163.9, 156.2, 143.6, 173.3, 135.2, 132.2, 131.1, 130.8, 130.4, 127.8, 126.4, 123.8, 123.4, 123.1, 114.1, 111.9, 111.8, 103.2, 56.5, 55.8, 45.4, 29.2. HRMS calcd. for $C_{22}H_{15}Br_2N_4$ (M+H): 492.9663, Found: 492.9691.

2-(3-Cyano-4,6-bis(4-iodophenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**36**): Yellow solid. Yield: 89%. Mixture (4/1 ratio) of **36/47**. IR (KBr, ν_{max}, cm^{-1}): 3441 (NH), 1589, 1548, 1429, 1261. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.77 (4H, app dd, *J* = 17 Hz, 8.8 Hz, Ar*H*), 7.07 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.96 (2H, d, *J* = 8.8 Hz, Ar*H*), 6.41 (1H, br s, NH), 3.37 (1H, d, *J* = 18 Hz, CH_2), 3.14 (1H, d, *J* = 18 Hz, CH_2), 1.77 (3H. s, CH_3). Data for minor isomer **47** where different from major isomer **36**, 7.75 (4H, app dd, *J* = 14 Hz, 8.8 Hz, Ar*H*), 7.02 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.88 (2H, d, *J* = 9.0, Ar*H*), 6.2 (1H, brs, C=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 164.8, 156.7, 140.9, 138.6, 138.6, 134.6, 129.1, 126.3, 114.3, 112.4, 112.2, 102.2, 99.8, 94.5, 56.6, 55.0 m, 45.1, 29.3. HRMS calcd. for $C_{22}H_{14}I_2N_4$ (M): 587.9308, Found: 587.9291.

2-(3-Cyano-4,6-bis(4-hydroxyphenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**37**): Orange solid. Yield: 75%. M.p.: 253-255 °C. IR (KBr, ν_{max}, cm^{-1}): 3382 (NH), 1575, 1510, 1435, 1261. ^{1}H NMR (300 MHz, DMSO): 10.55 (1H, br s, NH), 9.55 (1H, br s, ArO*H*), 9.45 (1H, br s, ArO*H*), 7.50 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.17 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.87 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.73 (2H, d, *J* = 8.4 Hz, Ar*H*), 3.75 (1H, d, *J*= 18 Hz, CH_2), 3.14 (1H, d, *J*= 18 Hz, CH_2), 1.65 (3H, s, CH_3). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 168.5, 161.9, 158.9, 156.5, 132.9, 131.4, 125.9, 125.5, 115.9, 115.8, 115.3, 115.2, 114.9, 97.3, 56.5, 48.1, 43.5, 28.8. HRMS calcd. for $C_{22}H_{16}N_4O_2$ (M): 368.1230, Found: 368.1273.

2-(3-Cyano-4,6-bis(3-hydroxyphenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**38**): Yellow solid. Yield: 93%. M.p.: 270-272 °C. IR (KBr, ν_{max}, cm^{-1}): 3449 (NH), 3250, 2213, 1594, 1451, 1429. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 9.92 (1H, br s, NH), 9.65 (1H, br s, ArO*H*), 9.55 (1H, br s, ArO*H*), 7.29 (1H, app t, *J* = 7.8 Hz, Ar*H*), 7.18 (1H, app t, *J* = 7.8 Hz, Ar*H*), 6.92 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.85-6.78 (3H, m, Ar*H*)), 6.70-6.65 (2H, m, Ar*H*), 3.61 (1H, d, *J*= 18 Hz, CH_2), 3.27 (1H, d, *J*= 18 Hz, CH_2), 1.67 (3H, s, CH_3). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 169.1, 157.9, 157.4, 157.3, 144.4, 136.8, 130.1, 1 29.7, 119.0, 118.8, 115.6, 115.5, 115.0, 114.8, 114.2, 113.7, 112.0, 100.7, 56.8, 49.1, 44.2, 28.4. HRMS calcd. for $C_{22}H_{16}N_4O_2$ (M): 368.1272, Found: 368.1273.

2-(3-Cyano-4,6-bis(4-methoxyphenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**41**): Brown solid. Yield: 77%. M.p.: 119-121 °C. IR (KBr, ν_{max}, cm^{-1}): 3449 (NH), 2926, 2212, 1510, 1459, 1259. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.45 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.15 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.91 (4H, app t, *J* = 9.4 Hz, Ar*H*), 6.73 (1H, br s, NH), 3.82 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.46 (1H, d, *J* = 18 Hz, CH_2), 3.05 (1H, d, *J* = 18 Hz, CH_2), 1.75 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.8, 163.2, 159.5, 157.9, 133.2, 130.5, 127.4, 125.7, 114.9, 114.7, 114.6, 113.6, 113.0, 99.4, 56.4, 55.6, 55.4, 55.0, 45.4, 29.2. HRMS Calcd. for $C_{24}H_{20}N_4O_2$ (M): 396.1586, Found: 396.1515.

2-(3-Cyano-4,6-bis(3-methoxyphenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**42**): Yellow solid. Yield: 80%. M.p.: 133-135 °C. IR (KBr, ν_{max}, cm^{-1}): 3449 (NH), 3284, 2212, 1598, 1427. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.34 (2H, app t, *J* = 8.0 Hz, Ar*H*), 7.01 (1H, app dd, *J* = 8.0 Hz, 2.0 Hz, Ar*H*), 6.93 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.87-6.79 (3H, m, Ar*H*), 6.73 (1H, app t, *J* = 2.1 Hz, Ar*H*), 6.38 (1H, br s, NH), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.45 (1H, d, *J* = 18 Hz, CH_2), 3.11 (1H, d, *J* = 18 Hz, CH_2), 1.77 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 166.3, 160.3, 157.1, 143.0, 136.7, 130.3, 120.2, 118.2, 116.6, 114.6, 113.2, 112.8, 112.7, 112.5, 111.5, 101.9, 67.1, 56.7, 55.5, 55.4, 45.5, 29.3. HRMS calcd. for $C_{24}H_{21}N_4O_2$ (M+H): 397.1665, Found: 397.1638

2-(3-Cyano-4,6-bis(4-nitrophenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**43**): Brown solid. Mixture (2/1 ratio) of **43/48**. IR (KBr, ν_{max}, cm^{-1}): 3447 (NH), 3419, 2963, 2928, 2188, 2160, 1596, 1520, 1453. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 9.68 (1H, br s, NH), 8.30 (2H, dd, *J* = 9.0 Hz, Ar*H*), 8.26 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.73 (2H d *J* = 9.0 Hz, Ar*H*), 7.62 (2H, d, *J* = 9.0 Hz, Ar*H*), 3.70 (1H, d, *J* = 18 Hz, CH_2), 3.53 (1H, d, *J* = 18 Hz, CH_2), 1.77 (3H, s, CH_3). Data for minor isomer **48** where different from major isomer **43**, 8.19 (4H, dd, *J* = 8.7 Hz, 5.4 Hz, Ar*H*), 7.68 (2H, d, *J* = 9.0 Hz, Ar*H*), 7.60 (2H, d, *J* = 9.0 Hz Ar*H*), 6.95 (1H, br s, C*H*=C), 1.61 (3H, s, CH_3) ^{13}C NMR (75 MHz, DMSO, δ, ppm): 166.1, 157.2, 156.5, 150.3, 148.8, 146.9, 146.7, 146.2, 145.4, 141.5, 135.5, 129.6, 128.9, 126.7, 125.8, 124.0, 123.8, 123.2, 123.1, 121.8, 120.6, 117.3, 115.1, 114.4, 112.7, 103.4, 57.1, 56.9, 51.1, 43.5, 30.1, 27.7. MS (ESI) calcd. for $C_{22}H_{15}N_6O_4$ (M+H): 427.1155, Found: 427.1130.

2-(3-Cyano-4,6-bis(3-nitrophenyl)-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (**44**): Brown solid. Yield: 80%. Mixture (2/1 ratio) of **44/49**. IR (KBr, ν_{max}, cm^{-1}): 3447 (NH), 3382, 3266, 2219, 2202, 1612, 1523, 1437. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 9.84 (1H, br s, NH), 8.37 (1H, app dt, *J* = 8.0 Hz, 2.0 Hz, Ar*H*), 8.33 (1H, br s, Ar*H*), 8.26 (2H, app d, *J* = 9.6 Hz, Ar*H*), 8.20-8.13 (3H, m, Ar*H*), 8.07 (1H, d, *J* = 8.0, Hz, Ar*H*), 7.94-7.89 (2H, m, Ar*H*), 7.84 (1H, app d, *J* = 3.6 Hz, Ar*H*), 7.80

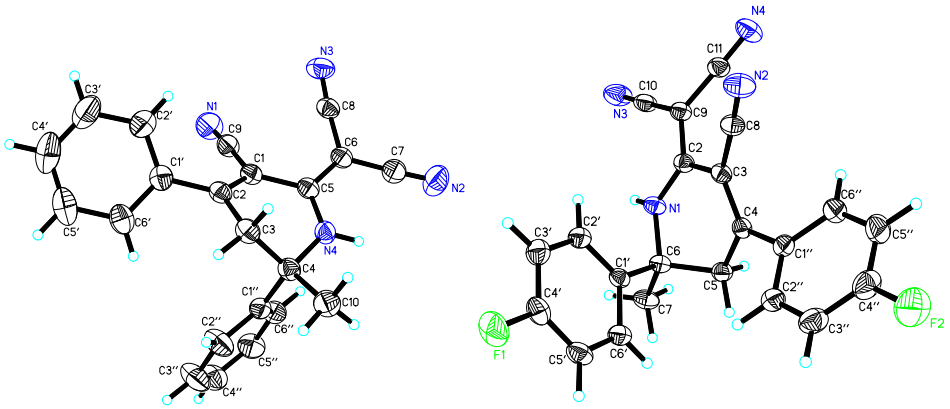


Figure 2. X-ray crystallographic structures of acetophenone dimer **28** and 4 fluoro dimer **30**.

(1H, d, *J* = 8.0 Hz, Ar*H*), 7.74 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.70-7.62 (3H, m, Ar*H*), , 3.90 (1H, d, *J* = 18 Hz, CH_2), 3.46 (1H, d, *J* = 18 Hz, CH_2), 1.78 (3H, s, CH_3). Data for minor isomer **44** where different from major isomer **49**, 6.97 (1H, br s, C*H*=C), 1.62 (3H, s, CH_3). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 165.6, 156.5, 148.1, 147.7, 147.6, 145.3, 140.3, 136.9, 134.4, 134.3, 131.8, 131.4, 130.8, 130.4, 129.6, 129.5, 126.1, 122.8, 122.7, 122.5, 121.9, 121.7, 121.6, 120.2, 119.4, 116.4, 115.2, 114.4, 112.9, 103.2, 56.8, 42.3, 30.3, 27.6. HRMS calcd. for $C_{22}H_{14}N_6O_4$ (M): 426.1077, Found: 426.1068.

2-(3-Cyano-4,6-bis(6-methoxynaphthalen-2-yl)-6-methyl-5,6-dihydropyridin-2(1H)-ylidene)malononitriles (**46**): Brown solid. Yield: 65%. M.p.: 148-150 °C. IR (KBr, ν_{max}, cm^{-1}): 3448 (NH), 2926, 2212, 1627, 1579, 1540, 1482, 1269. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.90 (1H, app d, *J* = 1.4 Hz, Ar*H*), 7.81 (1H, app d, *J* = 8.8 Hz, Ar*H*), 7.81 (3H, app d, *J* = 8.8 Hz, Ar*H*), 7.60 (1H, app d, *J* = 1.4 Hz, Ar*H*), 7.43 (1H, dd, *J* = 8.8 Hz, 2.0 Hz, Ar*H*), 7.38 (1H, dd, *J* = 8.8 Hz, 2.0 Hz, Ar*H*), 7.19 (2H, app td, *J* = 8.8 Hz, 2.8 Hz, Ar*H*), 7.12 (1H, d, *J* = 2.0 Hz, Ar*H*), 7.08 (6H, d, *J* = 2.4, Hz, Ar*H*), 6.49 (1H, br s, NH), 3.91 (6H, s, 2 x OCH_3), 3.70 (1H, d, *J* = 18 Hz, CH_2), 3.27 (1H, d, *J* = 18 Hz, CH_2), 1.89 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.2, 160.1, 158.6, 157.6, 136.6, 136.1, 134.2, 130.8, 130.3, 129.7, 129.4, 128.5, 128.0, 127.9, 127.8, 124.7, 123.6, 122.5, 120.4, 120.1, 114.9, 113.3, 112.8, 105.8, 105.6, 100.8, 56.8, 55.5, 55.4, 53.9, 45.4, 29.2. HRMS calcd. for $C_{32}H_{24}N_4O_2$ (M): 496.1939, Found: 496.1912.

3. Results and discussion

Towards our proposed synthetic target, we required to prepare the alkylidenemalononitriles **10**-**27** *via* an appropriate method to test the TBAF mediated cyclization conditions to form dicyano substituted dihydropyridine derivatives **28**-**46** (Scheme 1). The desired precursors **10**-**27** for this purpose were prepared from commercially available substituted acetophenone derivatives *via* Knoevenagel condensation with malononitrile by following the procedure developed by Barnes *et al.* [2] in good to excellent yield (50 to 95%).

The successful preparation of alkylidenemalononitriles **10**-**27** were enabled us to explore their dimerization under solvent-free conditions for the preparation of dicyano substituted dihydropyridine derivatives **28**-**46**. Initially, the phenyl alkylidenemalononitrile **10** was treated with neat TBAF.$3H_2O$ under solvent-free conditions to get the desire dimerized product **28** in low yield (20%) having molecular ion peak at *m/z* = 336. The next step involved, was the structure elucidation of this new compound. There are different possibilities in which the alkylidenemalononitrile could be dimerized to give different structures as shown in Scheme 1.

The ^{1}H NMR spectra of compound **28** showed four distinguished signals for four groups,
a) singlet for methyl group at δ_H = 1.79,
b) two doublets for two non-equivalent protons of methylene group at δ_H = 3.49, 3.15,
c) multiplet for aromatic protons between 7.24-7.50, and
d) broad singlet for NH group at δ_H = 6.58 ppm.

Interestingly, it has been observed that the value of NH group resonated between 6.00 to 9.50 ppm depends upon the solvent used to run the ^{1}H NMR spectrum. It shifted towards downfield region when ^{1}H NMR run in DMSO solvent and this was later confirmed by obtaining the ^{1}H NMR of 4-fluoro dimer **30** in both $CDCl_3$ (δ_H = 6.41 ppm) and DMSO (δ_H = 9.72 ppm). The above mentioned data is pretty much comparable with the reported data of structure **5** [22,23] and structure **8** [8]. Therefore, in order to solve the structural ambiguity, the compound was treated with NaOMe by using literature procedure to produce compound **6** by assuming the structure **5** of the new compound [24]. But the experiment proved to unsuccessful and we would not be able to obtain the desired compound **6**. The reaction mixture became very sluggish and even no starting material was recovered. Thus, with all these results, the X-ray crystallographic technique became obligatory to establish the structure of this new dimer. For this purpose, the compound was crystallized with little effort in the mixture of Ethanol/H_2O mixture and then X-ray crystallographic structure of compound **28** was then obtained which clearly showed the attachment of malononitrile group to the C-2 *via* double bond, cyano group at C-3 position, phenyl ring at C-4 position and quaternary center at C-6 position [8] (Figure 2). The X-ray crystallographic structure of the 4-flouro **30** derivative was also obtained for further verification (Figure 2).

All the spectroscopic data includes ^{1}H NMR, ^{13}C NMR, IR and mass spectra showed complete agreement with the structure **28**. After the confirmation of dimer structure **30**, the reaction condition was optimized to increase the yield of the reaction product. Initially, the temperature reaction mixture was raised from 35 to 85 °C and proceeded the reaction for 14 h until TLC analysis showed no starting material. The reaction mixture was cooled and quenched with 2.0 N HCl to get the compound **28** in excellent yield (95%) as a single product. The isolated product **28** was found to be analytically pure > 95% by ^{1}H NMR spectroscopy without tedious silica gel column chromatography. The scope of the reaction was further explored to prepare a range of dihydropyridine derivatives **28**-**46** in good to excellent yield (52 to 98%) as shown in the Table 1.

Table 1. Synthesis of functionalized dicyano substituted dihydropyridine **28-46** *via* TBAF-mediated dimerization.

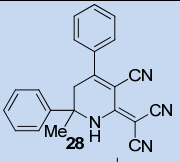
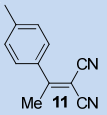
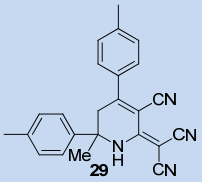
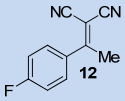
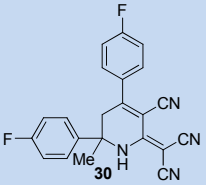
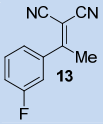
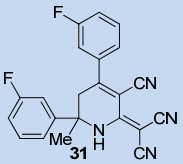
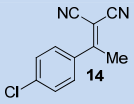
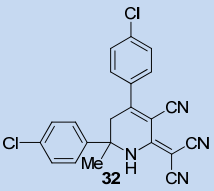
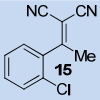
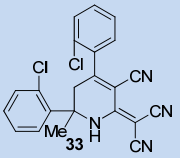
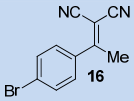
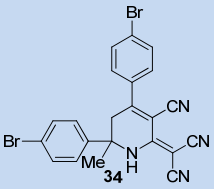
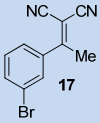
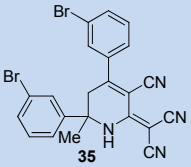
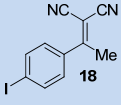
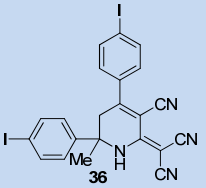
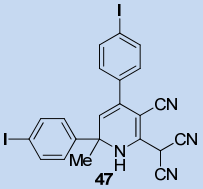
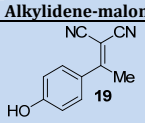
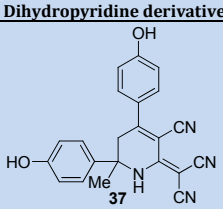
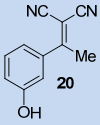
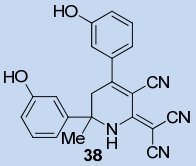
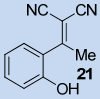
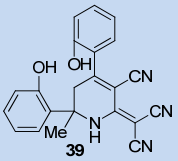
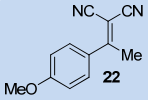
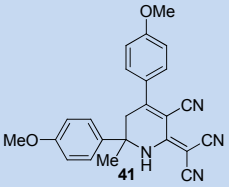
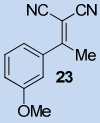
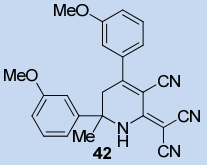
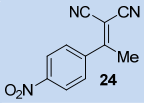
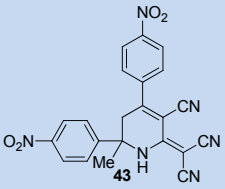
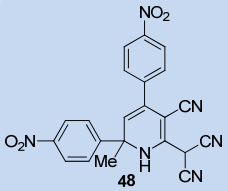
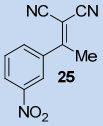
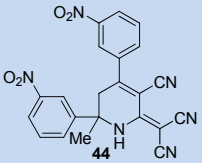
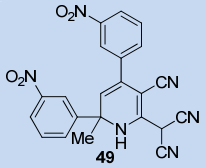
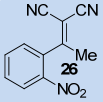
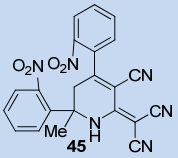
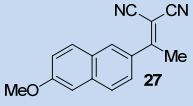
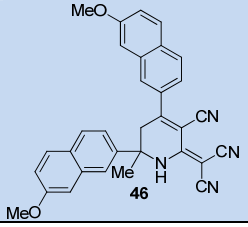
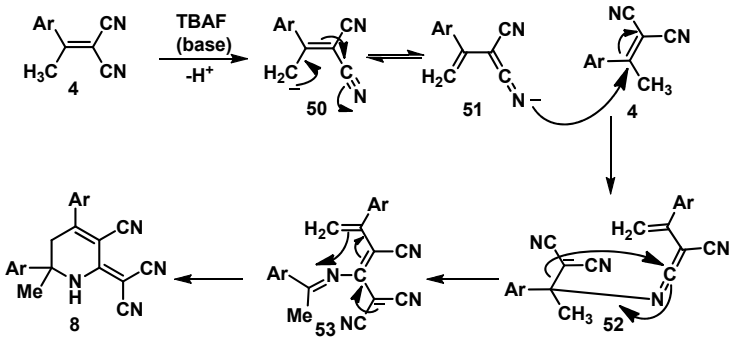
Entry	Alkylidene-malononitriles	Dihydropyridine derivatives	Dihydropyridine derivatives	Isolated Yield (%)
1	 **10**	 **28**	-	98
2	 **11**	 **29**	-	95
3	 **12**	 **30**	-	75
4	 **13**	 **31**	-	75
5	 **14**	 **32**	-	90
6	 **15**	 **33**	-	No reaction
7	 **16**	 **34**	-	90
8	 **17**	 **35**	-	90
9	 **18**	 **36**	 **47**	89 (4:1 ratio)

Table 1. (continued).

Entry	Alkylidene-malononitriles	Dihydropyridine derivatives	Dihydropyridine derivatives	Isolated Yield (%)
10			-	75
11			-	93
12			-	No reaction
13			-	95
14			-	80
16				52 (2:1 ratio)
17				80 (4:1 ratio)
18			-	No reaction
19			-	65



Scheme 2

The results presented in the Table 1 showed that in almost all cases we have only obtained dicyano substituted dihydropyridine derivatives **28**-**46** as single product in high yields. However, In the case of 4-iodo **18**, 4-nitro **24** and 3-nitro **25** derivatives, an inseparable mixture of corresponding dihydropyridines and their other derivatives were obtained in 4/1 to 2/1 ratio, as judged by ^{1}H NMR spectroscopy (Table 1). The dimerization of 2-chloro **15** ylidene, 2-hydroxy ylidene **21** and 2-nitro ylidene **26** was unsuccessful which could be possibly due to the steric interaction of methylene group, generated *in situ* deprotonation by TBAF, with the hydroxy and nitro substituents present at 2-position of the phenyl ring.

A plausible mechanism of this dimerization has been outlined in Scheme 2. The carbanion **50**, generated by the abstraction of proton from methyl group by TBAF which acts as base, rearrange itself to keteneimine **51** which then attacks to dicycano alkene **4** of another molecule to afford intermediate **52**. The intermediate **52** then undergo rearrangement to afford compound **53**, which on cyclization give final product **8** (Scheme 2) [7, 8].

4. Conclusion

In summary, we have successfully developed a new broad spectrum, eco-friendly method of alkylidenemalononitriles **10**-**27** dimerization to form the dihydropyridine derivative **28**-**46** under solvent-free conditions. TBAF is found to be an efficient base for promoting the reaction to desire products. Further work on other kind of ylidenes *e.g*. PhCH(CN)$_2$, further chemical transformations on above mentioned dimers **28**-**46** and their biological properties are under progress.

Acknowledgements

We are thankful to Higher Education Commission (HEC), Pakistan and Husein Ebrahim Jamal Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan for providing financial support.

Supplementary materials

CCDC-845736 (**28**) and 845735 (**30**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

References

[1]. Knoevenagel, K. *Ber. Dtsch. Chem. Ges.* **1988**, *31*, 2596-2619.
[2]. Barnes, D. M.; Haight, A. R.; Hameury, T.; Mclaughlin, M. A.; Mei, J.; Tedrow, J. S.; Toma, J. , D. R. *Tetrahedron* **2006**, *62*, 11311-11319.
[3]. Sharif, A.; Ahmad, E.; Munawar, M. A.; Jabeen, S.; Khan, M. U. A.; Begum, R.; Farrukh, A.; Ashraf, M.; Arshad, S.; Afza, N. *J. Chem. Soc. Pak.* **2011**, *33*, 578-786.
[4]. Bogdanowicz-Szwed, K.; Krasodomska, M. *Monatsh. Chem.* **2006**, *137*, 347-355.
[5]. Johnson, D. S.; Li, J. J. The Art of Drug Synthesis, John Wiley and Sons, Inc.: New Jersey, 2007.
[6]. Lichitsky, B. V.; Dudinov, A. A.; Krayushkin, M. M. *Arkivoc* **2001**, *9*, 73-79.
[7]. Dunkel, S.; Heb, U. *J. Prakt. Chem.* **1997**, *339*, 414-419.
[8]. Abdelrazek, F. M.; Metwally, M. H.; Kassab, N. A.; Sobhy, N. A.; Metz, P.; Jaeger, A. *J. Heterocyclic Chem.* **2010**, *47*, 348-388.
[9]. Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6192
[10]. Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216-3219.
[11]. Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *J. Org. Chem.* **1996**, *61*, 5013-5023.
[12]. Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. I* **1999**, 529-534.
[13]. Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron* **2001**, *57*, 9697-9710.
[14]. Chung, K. -H.; Moon, B. -C.; Lim, C. H.; Kim, J. P.; Lee, J. H.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 1203-1205.
[15]. Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 2896-2898.
[16]. Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*, 4951-4953.
[17]. Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Synlett.* **1999**, 199-200.
[18]. Albanese, D.; Donghi, A.; Landini, D.; Lupi, V.; Penso, M. *Green Chem.* **2003**, *5*, 367-369.
[19]. Lee, H. -G.; Won, J. -E.; Kim, M. -J.; Park, S. -E.; Jung, K. -J.; Kim, B. R.; Lee, S. -G.; Yoon, Y. -J. *J. Org. Chem.* **2009**, *74*, 5675-5678.
[20]. Sheldrick, G. M. SHELXTL/PC version 5. 1; Siemens Analytical X-ray Instruments Inc.: Madison, WI, 1997.
[21]. Johnson, C. K. ORTEPII. Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.
[22]. Nanjo, K.; Suzuki, K.; Sekiya, M. *Chem. Pharm. Bull.* **1977**, *25*, 2396-4000.
[23]. Ohnishi, Y.; Kagami, M.; Numakunai, T.; Ohno, A. *Chem. Lett.* **1976**, 915-916.
[24]. Quincoses, J.; Peseke, K. *Quim. Tecnol. Quim.* **1978**, *6*, 95-102.