Four-component reaction between trimethyl phosphite, aroyl chlorides and dialkyl acetylenedicarboxylate with benzoic acid hydrazide

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A four-component and one-pot reaction between trimethyl phosphite, a dialkyl acetylene dicarboxylate and an aroyl chloride with benzoic acid hydrazide is described as a simple and efficient route for the synthesis of functionalised pyrazoles in good yields.

Keywords: benzoic acid hydrazide, functionalised pyrazoles, dialkyl acetylene dicarboxylate, trimethyl phosphite, multi-component reaction

Substituted pyrazoles are known to possess a wide variety of biological activities including herbicidal,[1] anti-microbial,[2] anti-bacterial,[3] anti-inflammatory,[4] insecticidal,[5] analgesic,[6] and anti-pyretic[7] activity. 1,3,5-Tri- and 1,3,4,5-tetrasubstituted pyrazoles, which constitute the key structural units of major drugs, such as, Celebrex[8] and Acomplia[9] are of interest to the medicinal chemist.

The first method of the synthesis is 1,3,5-trisubstituted pyrazoles goes back to nineteenth century when Knorr employed 1,3-diketones and hydrazines as starting materials.[10] Since two isomeric products were formed from the reaction of hydrazines with unsymmetrical dicarbonyl compounds which were difficult to separate, efforts to replace the dicarbonyl compounds with olefinic or acetylenic ketones have been reported to develop regioselective syntheses of the pyrazole rings.[11] Although α,β-unsaturated ketones have been used as building blocks for the preparation of pyrazoles, vinylphosphonates have also been important synthetic intermediates[12] in these heterocycle syntheses.

The diastereoselective synthesis of a novel series of dialkyl (E)-2-(dialkoxyphosphoryl)-3-(aroyl)-2-butenedioate derivatives **(4)** using the reaction of trialkyl phosphite and an acetylenic ester with various aroyl chlorides via one-pot MCRs was reported in 2010.[13]

In continuation of our work on the reaction between trivalent phosphorus nucleophiles and acetylenic esters in the presence of organic NH, OH, or CH-acids,[14–23] we wish to report the results of our study on the reaction between trimethyl phosphite, dialkyl acetylenedicarboxylates and aroyl chlorides in the presence of benzoic acid hydrazide.

Results and discussion

Treatment of dialkyl acetylenedicarboxylates **(3),** trimethyl phosphite **(2)** and an aroyl chloride **(1)** with benzoic acid hydrazide in toluene under reflux and one-pot conditions leads to the formation of dialkyl 5-(aryl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylate **(5)** after 32 h in 63–80% yield. (Scheme 1)

Different aroyl chlorides were used to study the scope of the reaction,. As shown in Scheme 1, the reaction is compatible with aroyl chlorides substituted by electron-attracting groups such as nitro and or weakly electron-withdrawing group such as bromo. Using electron-releasing groups such as methoxy, no product was isolated.

The structures of compounds **5a–h** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The mass spectrum of compound **5a** showed the molecular ion peak at 409. The ^{1}H NMR spectrum of compound **5a** exhibited two single sharp lines readily recognised as arising from methoxy groups (δ = 3.63 and 3.82 ppm). The protons of the aromatic groups exhibited characteristic signals in the aromatic region of the spectrum. The ^{13}C NMR spectrum of compound **5a** showed 16 signals in agreement with the proposed structure. The IR spectrum of compound **5a** also supported the suggested structure. Strong absorption bands were observed at 1734 and 1691 cm^{-1} respectively for the ester and amide carbonyl groups.

A reasonable mechanism for the formation of compounds **5** is presented at Scheme 2.

On the basis of the well-established chemistry of acetylenic esters,[24–27] it is reasonable to assume that the functionalised pyrazole derivatives **5** arises from the initial addition of the phosphite **2** to the acetylenic ester **3** and subsequent attack of the resulting zwitterion **6** on the aroyl chloride **1** to yield the ion pair **7**. Then, attack of the chloride ion would yield the vinylphosphonate **4**. A conjugate addition of benzoic acid hydrazide to the reaction of unsaturated ketone **4** with takes place and is then followed by an expulsion of the phosphate to lead to the formation of intermediate **8** and **9**. The intermediate **9** undergoes cyclisation followed by the loss of water to form product **5**.

In summary dialkyl 5-(aryl)-1-phenyl-1*H*-pyrazole-3,4-dicarboxylates may be prepared by a simple, one-pot and four-component reaction between trimethyl phosphite, dialkyl acetylenedicarboxylates and aroyl chlorides with benzoic acid hydrazide in good yields. The present method has the advantage that the reaction is performed under neutral conditions and starting materials can be mixed without any activation or modification.

Experimental

Elemental analyses were performed at the analytical laboratory of Science and Research Unit of the Islamic Azad University. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer in solution in $CDCl_3$ using TMS as an internal standard. The chemicals employed in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of compounds **5a–h***: general procedure*

To a magnetically stirred solution of dialkyl acetylenedicarboxylate (1 mmol) and aroyl chloride (1 mmol) in toluene (5 mL) was added dropwise a solution of trimethyl phosphite (1 mmol) in toluene (3 mL) at room temperature over 10 min. The reaction mixture was then stirred for 8 h under reflux. Finally a solution of benzoic acid hydrazide (1 mmol) in toluene (5 mL) was added and the mixture was stirred for 24 h under reflux. Solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using a hexane–eethyl acetate mixture as eluent.

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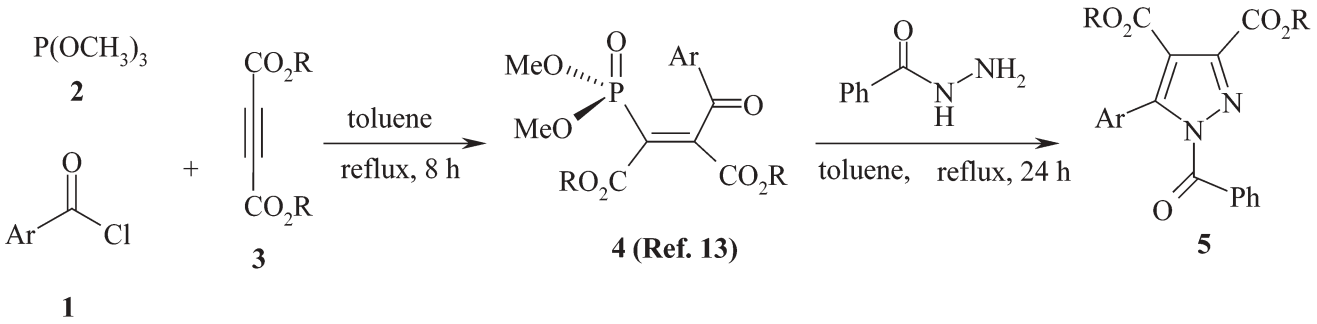
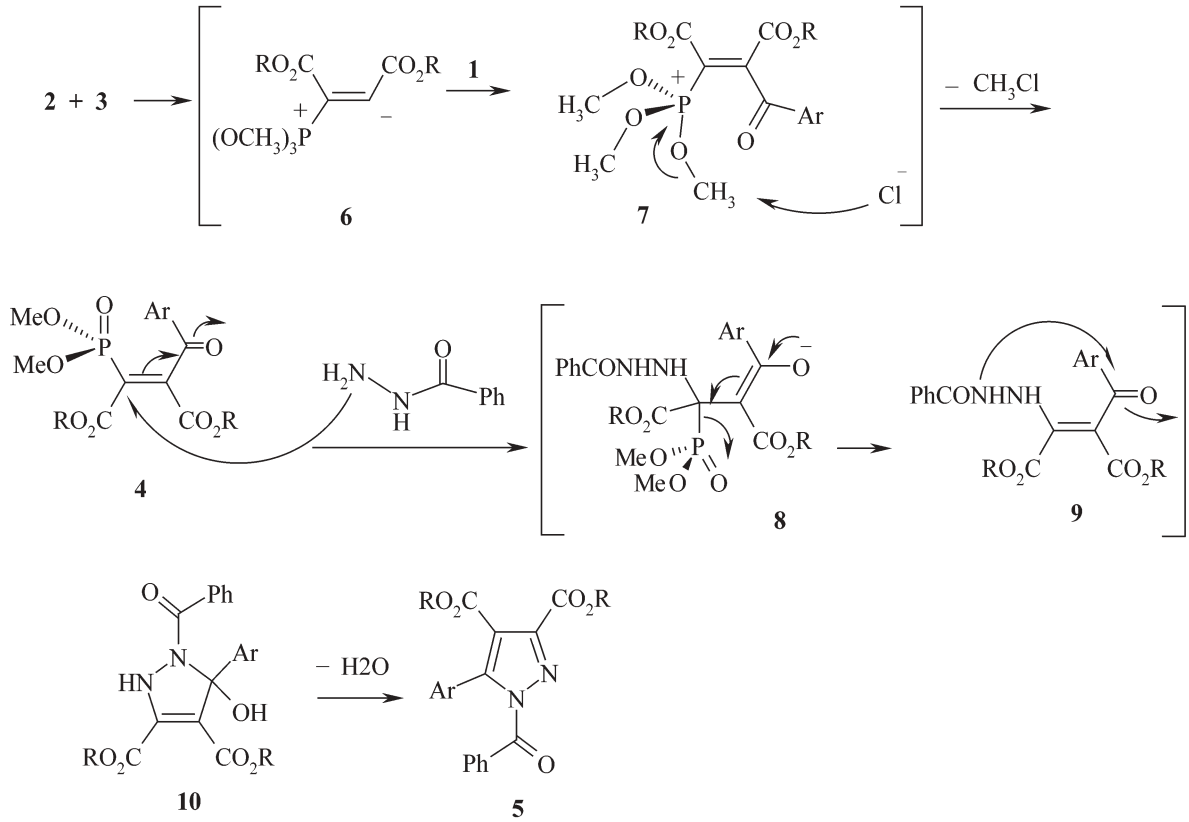


5	Ar	R	* %Yield
a	4-NO2 C_6H_4	CH_3	77
b	4-NO2 C_6H_4	*t*-Bu	68
c	4-Br C_6H_4	CH_3	75
d	4-Br C_6H_4	C_2H_5	72
e	3-$NO_2C_6H_4$	CH_3	80
f	2-$NO_2C_6H_4$	CH_3	75
g	2-Cl-5-NO_2 C_6H_3	CH_3	75
h	3-CO_2Me C_6H_4	CH_3	63

* Isolated yields

Scheme 1 Four-component reaction between aroyl chlorides, dialkyl acetylenedicarboxylate and trimethyl phosphite in the presence of benzoic acid hydrazide.



Scheme 2 Suggested mechanism for formation of compound **5**.

Dimethyl 5-(4-nitrophenyl)-1-phenyl-1H-pyrazole-3,4-dicarboxylate **(5a):** Yield: 77%; Yellow oil, IR (KBr) (ν_{max}/cm^{-1}): 1734 (C=O ester) and 1691 (C=O amide). MS, *m/z* (%): 409 (M^{+}, 4). Anal.Calcd for $C_{20}H_{15}N_3O_7$: C, 58.68; H, 3.69; N, 10.27. Found: C, 58.82; H, 3.55; N, 10.34%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 3.63, and 3.82 (6 H, 2 s, 2 OCH_3), 7.12–7.20 (5 H, m, 5 CH aromatic), 8.06 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of $C_6H_4NO_2$), 8.33 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of $C_6H_4NO_2$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 52.79 and 53.50 (2 OCH_3), 119.10 (C-5), 144.44 (C-4), 147.07 (C-3), 124.11, 127.66, 129.28, 129.57, 131.40, 132.91, 139.85 and 150.65 (aromatic), 162.98, 164.19, 166.17 (3C=O).

Di-t-butyl 5-(4-nitrophenyl)-1-phenyl-1H-pyrazole-3,4-dicarboxylate **(5b):** Yield: 68%; Yellow oil, IR (KBr) (ν_{max}/cm^{-1}): 1723 (C=O ester) and 1685 (C=O amide). MS, *m/z* (%): 493 (M^{+}, 3). Anal. Calcd for $C_{26}H_{27}N_3O_7$: C, 63.28; H, 5.51; N, 8.51. Found: C, 63.13; H, 5.59; N, 8.45%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): *δ* 0.85 and 1.42 (18 H, 2s, 6 CH_3), 7.08–7.35 (5 H, m, 5 CH aromatic), 8.08 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of $C_6H_4NO_2$), 8.23 (2 H, d, $^3J_{HH}$ = 8 Hz, 2 C*H* of $C_6H_4NO_2$) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): *δ* 28.65 and 28.67 (6 CH_3 of t-butyl groups), 87.28 and 81.80 (2 C of t-butyl groups), 120.98 (C-5), 143.74 (C-4), 144.32 (C-3), 125.86, 127.72, 129.74, 129.87, 130.05, 130.31, 138.08 and 150.16 (aromatic), 162.78, 164.26, 165.93 (3C=O).

Dimethyl 5-(4-bromophenyl)-1-phenyl-1H-pyrazole-3,4-dicarboxylate **(5c):** Yield: 75%; Yellow oil, IR (KBr) (ν_{max}/cm^{-1}): 1726 (C=O ester) and 1680 (C=O amide). MS, *m/z* (%): 442 (M^{+}, 11). Anal. Calcd for $C_{20}H_{15}BrN_2O_5$: C, 54.19; H, 3.41; N, 6.32. Found: C, 54.25; H, 3.57; N, 6.40%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 3.75, and 3.87 (6 H, 2 s, 2 OCH_3), 7.58–8.20 (5 H, m, 5 CH aromatic), 7.61 (2 H, d, $^3J_{HH}$ = 8 H_Z, 2 CH of C_6H_4Br), 8.21 (2 H, d, $^3J_{HH}$ = 8 H_Z, 2 CH of C_6H_4Br) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 51.52 and 52.86 (2 OCH_3), 120.39 (C-5), 144.54 (C-4), 147.25 (C-3), 124.02, 126.39, 129.26, 129.60, 131.59, 132.54, 138.34 and 150.44 (aromatic), 160.72, 163.84, 165.29 (3C=O).

Diethyl 5-(4-bromophenyl)-1-phenyl-1H-pyrazole-3,4-dicarboxylate **(5d):** Yield: 72%; Yellow oil, IR (KBr) (ν_{max}/cm^{-1}): 1726 (C=O ester) and 1687 (C=O amide). MS, *m/z* (%): 470 (M^{+}, 5). Anal.Calcd for $C_{22}H_{19}BrN_2O_5$: C, 56.07; H, 4.06; N, 5.94. Found: C, 56.18; H, 3.98; N, 6.14%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 0.92 and 1.32 (6 H, 2 t, $^3J_{HH}$ = 7 H_Z, 2CH_3), 4.26 and 4.42 (4 H, 2 q, $^3J_{HH}$ = 7 H_Z, 2OCH_2), 7.16–7.60 (5 H, m, 5 CH aromatic), 7.58 (2 H, d, $^3J_{HH}$ = 8 H_Z, 2 CH of C_6H_4Br), 8.19 (2 H, d, $^3J_{HH}$ = 8 H_Z, 2 CH of C_6H_4Br) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 14.34 and 14.71 (2CH3), 58.82 and 62.00 (2OCH2), 119.81 (C-5), 144.28 (C-4), 147.08 (C-3), 125.88, 127.69, 128.99, 129.20, 132.26, 132.67, 138.64 and 150.21 (aromatic), 162.68, 163.17, 165.03 (3C=O).

Dimethyl 5-(3-nitrophenyl)-1-phenyl-1H-pyrazole-3,4-dicarboxylate **(5e):** Yield: 80%; Yellow oil, IR (KBr) (ν_{max}/cm^{-1}): 1734 (C=O ester) and 1691 (C=O amide). MS, *m/z* (%): 409 (M^{+}, 9). Anal.Calcd for $C_{20}H_{15}N_3O_7$: C, 58.68; H, 3.69; N, 10.27. Found: C, 58.82; H, 3.55; N, 10.34%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 3.67, and 3.86 (6 H, 2 s, 2 OCH_3), 7.62–8.14 (9 H, m, 9 CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 52.85 and 53.57 (2 OCH_3), 119.16 (C-5), 144.42 (C-4), 147.15 (C-3), 121.51, 123.24, 129.28, 129.89, 130.58, 132.71, 134.23, 143.50, 148.61 and 150.65 (aromatic), 163.05, 164.28, 166.29 (3C=O).

Dimethyl 5-(2-nitrophenyl)-1-phenyl-1H-pyrazole-3,4-dicarboxylate **(5f):** Yield: 75%; Yellow oil, IR (KBr) (ν_{max}/cm^{-1}): 1734 (C=O ester) and 1691 (C=O amide). MS, *m/z* (%): 409 (M^{+}, 6). Anal.Calcd for $C_{20}H_{15}N_3O_7$: C, 58.68; H, 3.69; N, 10.27. Found: C, 58.82; H, 3.55; N, 10.34%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 3.59, and 3.75 (6 H, 2 s, 2 OCH_3), 7.52–7.91 (9 H, m, 9 CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 52.73 and 53.58 (2 OCH_3), 119.03 (C-5), 144.31 (C-4), 147.02 (C-3), 125.19, 127.62, 129.24, 129.93, 132.02, 133.87, 134.95, 139.82, 149.28 and 150.65 (aromatic), 162.91, 164.27, 166.12 (3C=O).

Dimethyl 5-(2-chloro-5-nitrophenyl)-1-phenyl-1H-pyrazole-3,4-dicarboxylate **(5g):** Yield: 75%; Yellow oil, IR (KBr) (ν_{max}/cm^{-1}): 1731 (C=O ester) and 1694 (C=O amide). MS, *m/z* (%): 443 (M^{+}, 11). Anal.Calcd for $C_{20}H_{14}ClN_3O_7$: C, 54.13; H, 3.18; N, 9.47. Found: C, 53.95; H, 3.02; N, 9.61%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 3.56, and 3.72 (6 H, 2 s, 2 OCH_3), 7.74–8.33 (8 H, m, 8 CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 52.67 and 53.44 (2 OCH_3), 118.85 (C-5), 144.16 (C-4), 146.93 (C-3), 123.62, 125.18, 127.60, 129.21, 129.76, 131.95, 140.00, 140.83, 147.36 and 150.65 (aromatic), 163.28, 164.32, 166.38 (3C=O).

Dimethyl 5-(3-methoxycarbonylphenyl)-1-phenyl-1H-pyrazole-3,4-dicarboxylate **(5h):** Yield: 63%; Yellow oil, IR (KBr) (ν_{max}/cm^{-1}): 1728 (C=O ester) and 1687 (C=O amide). MS, *m/z* (%): 422 (M^{+}, 3). Anal.Calcd for $C_{22}H_{18}N_2O_7$: C, 62.56; H, 4.30; N, 6.63. Found: C, 62.71; H, 4.25; N, 6.50%. ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si): δ 3.51, 3.63 and 3.82 (9 H, 3 s, 3 OCH_3), 7.42–7.98 (9 H, m, 9 CH aromatic) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$, Me_4Si): δ 51.89, 52.79 and 53.50 (3 OCH_3), 119.34 (C-5), 144.13 (C-4), 147.25 (C-3), 121.74, 123.55, 129.11, 129.65, 130.72, 132.88, 134.10, 143.63, 148.55 and 150.62 (aromatic), 162.80, 163.1, 166.25 (3C=O).

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References

1 S. Sugai, S. Mio, T. Honma and T.U.S. Sakamato, *Patent,* 1995, **5**, 424.
2 N.M. Abunada, H.M. Hassaneen, N.G. Kandile and O.A. Miqdad, *Molecules*, 2008, **13**, 1501.
3 A. Tanitame, Y. Oyamada, K. Ofuji, M. Fujimoto, K. Suzuki, T. Ueda, H. Terauchi, M. Kawasaki, K. Nagai, M. Wachi and J.I. Yamagishi, *Bioorg. Med. Chem*., 2004, **12**, 5515.
4 C. Selvam, S.M. Jachak, R. Thilagavathi and A.K. Chakraborti, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 1793.
5 R. Katoch-Rouse, L.A. Pavlova, T. Caulder, A.F. Hoffman, A.G. Mukhin and A.G.Horti, *J. Med. Chem.,* 2003, **46**, 642.
6 E.V. Shchegol'kov, O.G. Khudina, L.V. Anikina, Y.V. Burgart and V.I. Saloutin, *Khim.-Farm. Zh.,* 2006, **40**, 27.
7 T.D. Penning, J.J. Talley, S.R. Bertenshaw, J.S. Carter, P.W. Collins, S. Docter, M.J. Graneto, L.F. Lee, J.W. Malecha, J.M. Miyashiro, R.S. Rogers, D.J. Rogier, S.S. Yu, G.D. Anderson, E.G. Burton, J.N. Cogburn, S.A. Gregory, C.M. Koboldt, W.E. Perkins, K. Seibert, A.W. Veenhuizen, Y.Y. Zhang and P.C. Isakson, *J. Med. Chem.,* 1997, **40**, 1347.
8 T. Yoshioka, T. Fujita, T. Kanai, Y. Aizawa, T. Kurumada, K. Hasegawa and H. Horikoshi, *J. Med. Chem.,* 1989, **32**, 421.
9 L. Knorr, *Ber. Dtsch. Chem. Ges* ,1883, **16**, 2597.
10 X.J. Wang, J. Tan and K. Grozinger, *Tetrahedron Lett.,* 2000, **41**, 4713.
11 T. Minami and J. Motoyoshiya, *Synthesis* 1992, 333.
12 R. Kouno, T. Okauchi, M. Nakamura, J. Ichikawa and T. Minami, *J. Org. Chem.,*1998, **63**, 6239.
13 S. Rostamnia, A. Alisadeh and L.G. Zhu, *J. Comb. Chem.,* 2009, **11**, 143.
14 A. Hassanabadi, M.R. Hosseini-Tabatabaei, M. Shahraki M. Anary-Abbasinejad and S. Ghoroghchian, *J. Chem. Res.,* 2011, 11.
15 I. Yavari, M. Anary-Abbasinejad and Z. Hossaini, *Org. Biomol. Chem*., 2003, **3**, 560.
16 M. Anary-abbasinejad aand N. Ascarrian, *J. Chem. Res.,* 2007, 11.
17 M. Anary-Abbasinejad, N. Rostami, A. Parhami and A. Hassanabadi, *J. Chem. Res.,* 2007, 257.
18 M. Anary-Abbasinejad, A. Hassanabadi and H. Anaraki-Ardakani, *J. Chem. Res.,* 2007, 455.
19 M. Anary-Abbasinejad and A. Hassanabadi, *J. Chem. Res.,* 2007, 475.
20 M. Anary-Abbasinejad, H. Anaraki-Ardakani, A. Dehghan, A. Hassanabadi and M.R. Seyedmir, *J. Chem. Res.,* 2007, 574.
21 M. Anary-Abbasinejad, A. Hassanabadi and M. Mazraeh-Seffid, *J. Chem. Res.,* 2007, 708.
22 M. Anary-Abbasinejad, K. Charkhati and A. Hassanabadi, *J. Chem. Res*., 2009, 319.
23 M.H. Mosslemin, M. Anary-Abbasinejad, A. Hassanabadi and M.A. Bagheri, *J. Sulfur. Chem*., 2010, **31**, 135.
24 I. Ugi, *Pure Appl. Chem.,* 2001, **77**, 187.
25 M.C. Bagley, J.W. Cale and J. Bower, *Chem. Commun*., 2002, 1682.
26 U. Bora, A. Saikia and R.C. Boruah, *Org. Lett*., 2003, **5**, 435.
27 I. Yavari, H. Djahaniani and F. Nasiri, *Tetrahedron*, 2003, **59**, 9409.