Article

J. Mex. Chem. Soc. **2011**, *55(4),* 238-241

ISSN 1870-249X

One-Pot Regioselective Synthesis of 4-Bromopyrazole Derivatives Under Solvent Free Conditions

Heshmatollah Alinezhad,* Mahmood Tajbakhsh, and Mahboobeh Zare

Faculty of Chemistry, Mazandaran University, Babolsar, Iran. heshmat@umz.ac.ir.

Received June 2, 2011; accepted September 2, 2011

Abstract. An efficient protocol for the one pot regioselective synthesis of 4-bromopyrazole derivatives from 1,3-diketones, arylhydrazines and *N*-bromosaccharin, in the presence of silica gel supported sulfuric acid as heterogeneous catalyst, under solvent free conditions, is reported.
Key words: 4-bromopyrazole, solvent free, *N*-bromosaccharin, 1,3-diketone, arylhydrazine.

Resumen. En este trabajo se informa de un método nuevo y eficiente para la síntesis regioselectiva y en una sola etapa de derivados del 4-bromopirazol, a partir de 1,3- dicetonas, arilhidracinas y *N*-bromosacarina empleando como catalizador ácido sulfúrico soportado en gel de sílice, en ausencia de disolvente.
Palabras clave: 4-bromopirazol, libre de solventes, *N*-bromosacarina, 1,3-dicetona, arilhidracina.

Introduction

Pyrazole ring systems have received more and more attention in the recent years because they have proven to be extremely useful intermediates for the synthesis of new biologically active compounds [1]. Brominated pyrazoles are useful either as synthetic intermediates in transition metal catalyzed cross-coupling reactions, such as Heck, Stille, Suzuki, Sonogashira, and Negishi, this in addition to their use as couplings or targets in the search for pharmacologically active compounds, such as antidiabetic and bradykinin B1 receptor antagonists [2,3].

A variety of synthetic methods for the preparation of brominated pyrazoles have been reported [4]. One of the most common procedures is bromination of pyrazoles [5], which is usually carried out in organic solvents, requiring often excess amount of brominating agent and multistep synthesis in order to access to an appropriated substituted pyrazole, when it is not commercially available [2, 6].

Recently, several improved protocols for the synthesis of pyrazoles have been reported by modification of classical condensation of 1,3-diketones and hydrazines using concentrated H_2SO_4[7] and silica-supported sulfuric acid [8] under solvent free conditions, fluorinated alcohols [9] and water [10] as solvent and under microwave irradiation [11].

Different brominating agents such as NBS [12], elemental bromine [13] and KBr [14] have been previously used for the bromination of pyrazole derivatives.

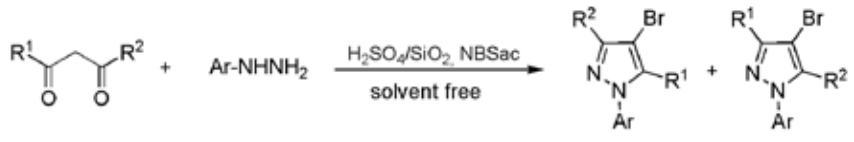
N-bromosuccharin, is a stable solid, easily prepared from saccharin and is much more reactive than its analogue NBS, which is applied as an oxidant and as brominating agent for some aromatic compounds [15].

On the other hand one-pot solvent-free reactions are economically and environmentally advantageous because of reducing amounts of waste and enhancing synthesis efficiency [16, 17]. In addition, solvent-free reactions are often rapid, regio- or chemoselective and occur in higher yields than reactions in organic solvents [7].

Thus, in this work is reported a facile one-pot regioselective preparation of 4-bromopyrazoles from 1,3-diketones, arylhdrazines and *N*-bromosaccharin (NBSac) in the presence of silica gel supported sulfuric acid (H_2SO_4/SiO_2) under solvent free conditions (Scheme 1).

Results and Discussion

In preliminary experiments, acetylacetone and phenylhydrazine were selected as substrates in order to obtain appropriated reaction conditions. When an equimolar amount of acetylacetone and phenylhydrazine in the presence of 0.01 g of H_2SO_4/SiO_2 were ground at room temperature, the conversion was fulfilled and 3, 5-dimethyl-*N*-phenylpyrazole was obtained. To this mixture one equivalent of *N*-bromosaccharin was added and mixed thoroughly; in this sense the target 3,5-dimethyl-4-bromo-*N*-



1, R^1 = alkyl, aryl, CF_3 R^2 = alkyl **2** **3a-l** **4a-l**

Scheme 1.

phenylpyrazole was obtained in excellent yield within 7 min (Table 1, entry1).

To examine the generality and applicability of this protocol various symmetrical and unsymmetrical 1,3-diketones and several arylhydrazines were assayed with *N*-bromosaccharin in the presence of H_2SO_4/SiO_2, the corresponding results are shown in Table 1.

As indicated in this Table, the reactions of acetylacetone and various arylhydrazines with NBSac under optimal reaction conditions afforded 4-bromo-3, 5-dimethyl-*N*-arylpyrazoles in excellent yields (entries 1-4). Similarly benzoylacetone as an unsymmetrical 1,3-diketone reacted with arylhydrazines and then brominated in one-pot to give the corresponding 4-bromopyrazoles in high yields (entries 5-8).

Due to agrochemical and pharmaceutical properties of pyrazole derivatives containing CF_3 group [18], the reaction of 1,1,1-trifluoropentane-2, 4-dione with arylhydrazines (scheme 2) were also evaluated. When we treated 1,1,1-trifluoropentane-2, 4-dione was treated with phenylhydrazine under optimal reaction conditions, two products were identified: 3-trifluoroarylpyrazole **(5)** and 5-hydroxy-5-trifluoroarylpyrazoline **(6)** (Scheme 2)**.**

The compound **6** (Ar = Ph) does not eliminate water and can be isolated as stable solid which is probably due to destabilization of CF_3 group on the formation of an incipient carbocation character at C-5 position [19]. However, when the reaction temperature reached 50-60 ^oC 3-trifluorophenylpyrazole and 5-trifluorophenylpyrazole were obtained in less than 1 min, which then brominated with NBSac under solventless conditions as mentioned above (entry 9). The corresponding brominated compounds were separated and then characterized by their corresponding spectral data, the appearance of signals at δ −56.59 and −62.53 ppm in the ^{19}F NMR of the products confirmed their structures (see experimental section). Under these conditions, various arylhydrazines, 1,1,1-trifluoropentane-2,4-dione and NBSac were successfully converted to the corresponding regioisomers of 4-bromo arylpyrazoles in high yields (entries 10-12).

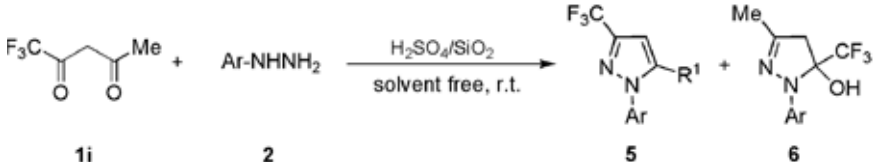
In order to compare the reactivity of NBSac with *N*-bromosuccinimide (NBS), in this reaction, some experiments were repeated using NBS under optimal reaction conditions, Scheme 3.

It is clear from Scheme 3 that NBS shows similar activity in the reactions of acetylacetone with phenylhydrazine or *p*-chlorophenylhydrazine (Scheme 3, entries 1, 2). In the case of 1,1,1-trifluoropentane-2,4-dione reaction was very slow, sluggish and only 34% of the products together with unbrominated pyrazoles, which were detected by ^{1}HNMR of the crude product (Scheme 3, entry 3). Integration of the signals at δ 6.48 and 6.62 ppm attributed to the proton of the unbrominated pyrazoles ring and signals δ at 2.36 and 2.37 ppm for the methyl groups of the brominated products in the ^{1}H NMR confirmed the ratio of the crude mixture.

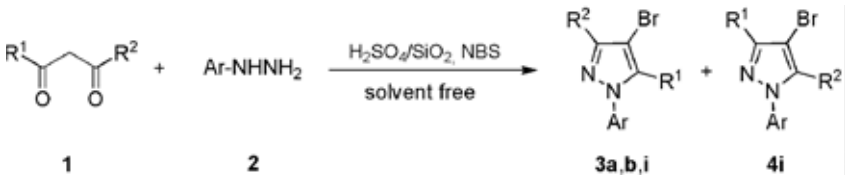
Table 1. Preparation of 4-bromo-1,3,5-trisubstituted pyrazoles by *N*-bromosaccharin.

entry	R^1	R^2	Ar	T(^{0}C)	Time (min)	Product Yield(%)[a]
1	Me	Me	Ph	RT	7	3a (98)
2	Me	Me	*p*-ClC_6H_4	RT	10	3b(96)
3	Me	Me	*o*-ClC_6H_4	RT	8	3c (95)
4	Me	Me	*p*-$OMeC_6H_4$	RT	< 1	3d (96)
5	Ph	Me	Ph	RT	15	3e (90)
6	Ph	Me	*p*-ClC_6H_4	RT	40	3f (90)
7	Ph	Me	*o*-ClC_6H_4	RT	20	3g (91)
8	Ph	Me	*p*-$OMeC_6H_4$	RT	10	3h (94)
9	CF_3	Me	Ph	50-60	< 1	3i+4i (15:80)
10	CF_3	Me	*p*-ClC_6H_4	50-60	< 1	3j+4j (10:78)
11	CF_3	Me	*o*-ClC_6H_4	50-60	< 1	3k+4k (15:80)
12	CF_3	Me	*p*-$OMeC_6H_4$	50-60	< 1	3l+4l (10:82)

[a] Isolated yield.



Scheme 2.



1 **2** **3a,b,i** **4i**

entry	R^1	R^2	Ar	T(^{0}C)	Time (min)	Product Yield (%)
1	Me	Me	Ph	RT	7	3a (97) [a]
2	Me	Me	*p*-ClC_6H_4	RT	10	3b (96) [a]
3	CF_3	Me	Ph	50-60	120	3i+4i (24) [b]

[a] Isolated yield.
[b] NMR yield.

Scheme 3.

In this study, a one pot, new and regioselective procedure to achieve with high yield various 4-boromopyrazole derivatives under solvent free conditions, was afforded. The use of silica gel supported sulfuric acid as a stable catalyst, an inexpensive and efficient brominating agent (NBSac), one-pot and solvent free conditions are important additional eco-friendly attributes of this synthetic protocol; thus a good green approach is offered.

Experimental

Materials were purchased from Fluka and Merck companies. H_2SO_4/SiO_2 [20] and NBSac [21] were prepared according to the reported procedure. The structure of all products were characterized by spectral data (^{1}H NMR, ^{13}C NMR, ^{19}F NMR and IR) and elemental analysis (CHN).

1,3 diketones (1 mmol) and arylhydrazines (1 mmol) were ground with H_2SO_4/SiO_2 (0.01 g) in a pestle mortar and then the mixture was ground at room temperature under solvent free conditions at room temperature. In the case of 1,1,1-trifluoropentane-2,4-dione, hydrazines were slowly added to a mixture of 1,1,1-trifluoropentane-2,4-dione and H_2SO_4/SiO_2 at 0 ^{0}C and then the mixture were stirred at 50-60 ^{0}C temperature. After completion of the cyclocondenstion of 1,3 diketone to pyrazole, stoichiometric amounts of NBSac (1 mmol) was added at appropriate temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, *n*-hexane (7-10 ml) was added to the mixture and filtered off. The residue was washed with *n*-hexane and evaporation of solvent afforded pure 4-bromopyrazole derivative. If necessary the product was further purified by column chromatography on silica gel.

Spectral data of all products are as follows:

3a: oil; IR (liquid film) ν (cm^{-1}) 3069, 2933, 1507,1426, 1375, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H, Me), 2.31 (s, 3H, Me), 7.36-7.40 (m, 3H, Ph), 7.44-7.45 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.77, 12.38, 96.38, 124.66, 127.81, 129.17, 137.50, 139.81, 147.56; *Anal* C 52.59%, H 4.4%, N 11.18%, Calcd C 52.61%, H 4.42%, N 11.16%.

3b: oil; IR (liquid film) ν (cm^{-1}) 3040, 2965, 1416, 1376, 1062, 1012; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H, Me), 2.31 (s, 3H, Me), 7. 34 (d, *J*= 9Hz, 2H, Ph), 7.43 (d, *J*= 9Hz, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.80, 12.36, 96.85, 125.72, 129.34, 133.51, 137.51, 138.31, 147.99; *Anal.* C 46.22%, H 3.52%, N 9.88%, Calcd C 46.26%, H 3.53%, N 9.81%.

3c: oil; IR (liquid film) ν (cm^{-1}) 3094, 2923, 1542, 1562, 1507, 1456, 1072, 1047; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H, Me), 2.30 (s, 3H, Me), 7. 41-7.34 (m, 4H, Ph), ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.75, 12.45, 95.24, 127.69, 129.78, 130.29, 130.58, 132.32, 137.28, 139.39, 147.97; *Anal.* C 46.24%, H 3.57%, N 9.80%, Calcd C 46.26% , H 3.53%, N 9.81.

3d: oil; IR (liquid film) ν (cm^{-1}) 3051, 2998, 1522, 1466, 1254, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H, Me), 2.30 (s, 3H, Me), 3.85 (s, 3H, Me), 7.28 (d, *J*= 9Hz, 2H, Ph), 7.45 (d, *J*= 9Hz, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$); δ 12.21, 20.15, 55.59. 97.74, 114.48, 126.36, 132.81, 137.71, 159.75, 171.17; *Anal.* C 51.30%, H 4.60%, N 9.95, Calcd C 51.26%, H 4.66%, N 9.96%.

3e: mp 70-73 °C; IR (liquid film) ν (cm^{-1}) 3064, 2928, 1507, 1362, 1225, 1070; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H, Me), 7.18-7.31 (m, 10H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) 12.54, 96.90, 124.699, 127.308, 128.45, 128.80, 128.87, 129.00, 129.13, 129.26, 129.88, 139.89, 140.68, 148.48; *Anal.* C 61.32%, H 4.22%, N 8.91. Calcd C 61.36%, H 4.18%, N 8.94.

3f: mp120-122 °C; IR (liquid film) ν (cm^{-1}) 3059, 2928, 1497, 1360, 1062; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, Me), 7.14 (d, *J*= 9Hz, 2H, Ph) 7.23-7.29 (m, 4H, Ph), 7.37-7.40 (m, 3H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) 12.54, 97.35, 125.67, 128.63, 128.85, 129.02, 129.84, 132.905, 138.39, 140.71, 148.84, 155.82; *Anal.* C 55.22%, H 3.40%, N 8.10%, Calcd C 55.28%, H 3.48%, N 8.06%.

3g: oil; IR (liquid film) ν (cm^{-1}) 3080, 2978, 1547, 1512, 1221, 1062; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H, Me), 7.29-7.39 (m, 9H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): 12.66, 95.64, 127.41, 128.28, 128.53, 128.78, 129.37, 130.00, 130.22, 130.29, 132.23, 137.81, 142.59, 148.89; *Anal.* C 55.22%, H 3.40%, N 8.10%, Calcd C 55.28 %, H 3.48%, N 8.06%.

3h: mp 95-98 °C; IR (liquid film) ν (cm^{-1}) 3064, 2943, 1517, 1451, 1249, 1062, 1031; ^1H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H, Me), 3.78 (s, 3H, Me), 6.80 (d, *J*= 9Hz, 2H, Ph), 7.12 (d, J= 9Hz, 2H, Ph), 7.25-7.30 (m, 2H, Ph), 7.30-7.36 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): 12.52, 55.45, 96.22, 114.01, 126.18, 128.39, 128.68, 129.88, 133.171, 140.63, 148.01, 158.17; *Anal.* C 59.44%, H 4.42%, N 8.18%, Calcd C 59.49 %, H 4.41%, N 8.16%.

4i: oil; IR (liquid film) ν (cm^{-1}) 3060, 2926, 2863, 1600, 1494, 1240, 1182, 1140, 1071. ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, Me), 7.34-7.45 (m, 2H, Ph), 7. 49-7.59 (m, 3H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.53; *Anal.* C 43.34%, H 2.63%, N 9.13%, Calcd C 43.30%, H 2.62%, N 9.18%.

3i: oil; IR (liquid film) ν (cm^{-1}) 3006, 2958, 2863, 1600, 1504, 1467, 1293, 1182, 1134, 1071; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H, Me), 7. 41-7.54 (m, 2H, Ph), 7. 48-7.50, (m, 3H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.59 ; *Anal.* C 43.32%, H 2.60%, N 9.15%, Calcd C 43.30%, H 2.62%, N 9.18%.

4j: oil; IR (liquid film) ν (cm^{-1}) 3016, 2939, 2003, 1499, 1288, 1182, 1140, 1033; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, Me), 7.40 (d, *J*= 9Hz, 2H, Ph), 7.51 (d, *J*= 9Hz, 2H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.65; *Anal.* C 36.94%, H 2.02%, N 8.21%, Calcd C 38.91%, H 2.08%, N 8.25%.

3j: oil; IR (liquid film) ν (cm^{-1}) 3019, 2958, 2931, 1501, 1486, 1287, 1221, 1183, 1139; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H, Me), 7.40 (d, *J*= 9Hz, 2H, Ph), 7.51 (d, *J*= 9Hz, 2H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.51; *Anal.* C 38.94%, H 2.03%, N 8.22%, Calcd C 38.91 %, H 2.08%, N 8.25%.

4k: oil; IR (liquid film) ν (cm^{-1}) 3063, 2931, 1495, 1386, 1232, 1186, 1139, 1052; ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, Me), 7.28-7.60 (m, 4H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.64; *Anal.* C 38.90%, H 2.02%, N 8.28%, Calcd C 38.91 %, H 2.08%, N 8.25%.

3k: oil; IR (liquid film) ν (cm^{-1}) 3069, 2926, 1504, 1462, 1303, 1224, 1187, 1140, 1066; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H, Me), 7.40-7.57 (m, 4H, Ph) ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.65; *Anal.* C 38.90%, H 2.04%, N 8.26%, Calcd C 38.91%, H 2.08%, N 8.25%.

4l: oil; IR (liquid film) ν (cm^{-1}) 3016, 2963, 1522, 1256, 1137, 1035; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H, Me), 3.88 (s, 3H, Me),7.02 (d, *J*= 9Hz, 2H, Ph), 7.34 (d, *J*= 9Hz, 2H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.47; *Anal.* C 43.08%, H 3.03%, N 8.30%, Calcd C 43.01%, H 3.01%, N 8.36%.

3l: oil; IR (liquid film) ν (cm^{-1}) 3020, 2932, 1515, 1240, 1140, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H, Me), 3.98 (s, 3H, Me),7.02 (d, *J*= 9Hz, 2H, Ph), 7.34 (d, *J*= 9Hz, 2H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.59; *Anal.* C 43.07%, H 3.01%, N 8.31%, Calcd C 43.01 %, H 3.01%, N 8.36%.

Acknowledgement

This work was supported by Research Grant from Mazandaran University, Iran.

References

1. (a) Gioiello, A.; Khamidullina, A.; Fulco, M. C.; Venturoni, F.; Zlotsky, S.; Pellicciari, R. *Tetrahedron Lett*. **2009**, *50*, 5978-5980. (b) Ouyang, G.; Cai, X. J.; Chen, Z.; Song, B. A.; Bhadury, P. S.; Yang, S.; Jin, L. H.; Xue, W.; Hu, D.Y.; Zeng, S. *J. Agric. Food Chem.* **2008**, *56,* 10160–10167.
2. Li, G.; Kakarla, R.; Gerritz, S. W. *Tetrahedron Lett*. **2007**, *48*, 4595-5499.
3. Salaheldin, A. M.; Oliveira-Campos, A. M. F.; Rodrigues, L. M. *Tetrahedron Lett*. **2007**, *48*, 8819-8822.
4. (a) Wang, X. J.; Tan, J.; Grozinger, K. *Tetrahedron Lett*. **2000**, *41*, 4713-4716 (b) Itoh, N.; Izumi. Y.; Yamada, H. *Biochemistry* **1987**, *26*, 282–289. (c) Foti, F.; Grassi, G.; Risitano, F. *Tetrahedron Lett*. **1999**, *40*, 2605-2606.
5. Stefani, H. A.; Pereira, C. M. P.; Almeida, R. B.; Braga, R. C.; Guzen, K. P.; Cella, R. *Tetrahedron Lett*. **2005**, *46*, 6833-6837. (b) Day, R. A.; Blake, J. A.; Stephens, C. E. *Synthesis* **2003**, *10*, 1586-1590.
6. Jeon, S. L.; Choi, J. H.; Kim, B. T.; Jeong, I. H. *J. Fluorine Chem*. **2007**, *128*, 1191-1197.
7. Wang, Z. X.; Qin, H.L. *Green Chem*. **2004**, *6*, 90-92.
8. Chen, X.; She, J.; Shang, Z. C.; Wu, J.; Zhang, P. *Synth. Commun* **2009**, *39,* 947-957.
9. Fustero, S.; Roman, R.; Sanz-Cervera, J. F.; Simon-Fuentes, A.; Cunat, A. C.; Villanova, S.; Murguia M. *J. Org. Chem*. **2008**, *73*, 3523-3529.
10. Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett*. **2008**, *49*, 397-400.
11. Bouabdallah, I.; Touzani, R.; Zidane, I.; Ramdani, A.; Radi, S. *Arkivoc part (xii)*. **2006**, 138-144.
12. (a) Martins, M. A. P.; Scapin, E.; Frizzo, C. P.; Rosa, F. A.; Bonacorso, H. G.; Zanatta, N. *J. Braz. Chem. Soc*. **2009**, *20*, 205-213. (b) Dwyer, M. P.; Paruch, K.; Alvarez, C.; Doll, R. J.; Keertikar, K.; Duca, J.; Fischmann, T. O.; Hruza, A.; Madison, V.; Lees, E.; Parry, D.; Seghezzi, W.; Sgambellone, N.; Shanahan, F.; Wiswell, D.; Guzi T. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6216-6219.
13. Schlosser. M.; *Angew. Chem. Int. Ed.* **2006**, *45*, 5432–5446.
14. Havanur, S.; Badami, B.V.; Puranik, G.S. *Can .J. Chem*. **1983**, *61*, 154-155.
15. Firouzabadi, H.; Iranpoor, N.; Ebrahimzadeh. F. *Tetrahedron Lett*. **2006**, *47*, 1771-1775.
16. Ballini, R.; Palmieri A.; Righi, P. *Tetrahedron* **2007**, *63*, 12099-12121.
17. Alinezhad, H.; Tajbakhsh, M.; Zare M. *Synth. Commun.* **2009***, 39*, 2907-2916.
18. Touzot, A.; Soufyane, M.; Berber, H.; Toupet, L.; Mirand, C. *J. Fluorine Chem*. **2004**, *125*, 1299-1304.
19. Song, L. P.; Zhu, S. Z. *J. Fluorine Chem*. **2001**, *111*, 201-205.
20. Lakouraj, M. M.; Akbari, A. *Indian. J. Chem, B*. **2003**, 1165-1167.
21. Souza, S. P. L.; Silva, J. F. M.; Mattos, M. C. S. *Synth. Commun*. **2003**, *33*, 935-939.