Iranian Journal of Organic Chemistry Vol. 6, No. 1 (2014) 1197-1202

A green and novel three-component one-pot synthesis of tetrahydrobenzopyran, pyrano[2,3-d]pyrimidine, and 3,4-dihydropyrano[c]chromene derivatives using sodium acetate

Malek Taher Maghsoodlou*, Mohyeddin Safarzaei, Mir Rasul Mousavi, Nourallah Hazeri, Jasem Aboonajmi and Moheb Shirzaei

Department of Chemistry, Faculty of Science, University of Sistan & Baluchestan, P. O. Box 98135-674 Zahedan, Iran.

Received: November 2013; Revised: November 2013; Accepted: January 2014

Abstract: Sodium acetate effectively catalyzes the three-component reaction between arylaldehydes, malononitrile, and 1,3-dicabonyl compounds such as dimedone, 4-hydroxycoumarin, barbituric acid, and thiobarbituric acid for the formation of corresponding pyran annulated heterocyclic systems. This green method offers the advantages of proceeding, neutral and mild conditions, environmental, lock of toxicity, short reaction time, giving high to excellent yields of the products, and simple work-up.

Keywords: Multicomponent reaction, Pyran annulared, 1,3-Dicabonyl compound, Barbituric acid, Hydroxycoumarin, Aromatic aldehyde.

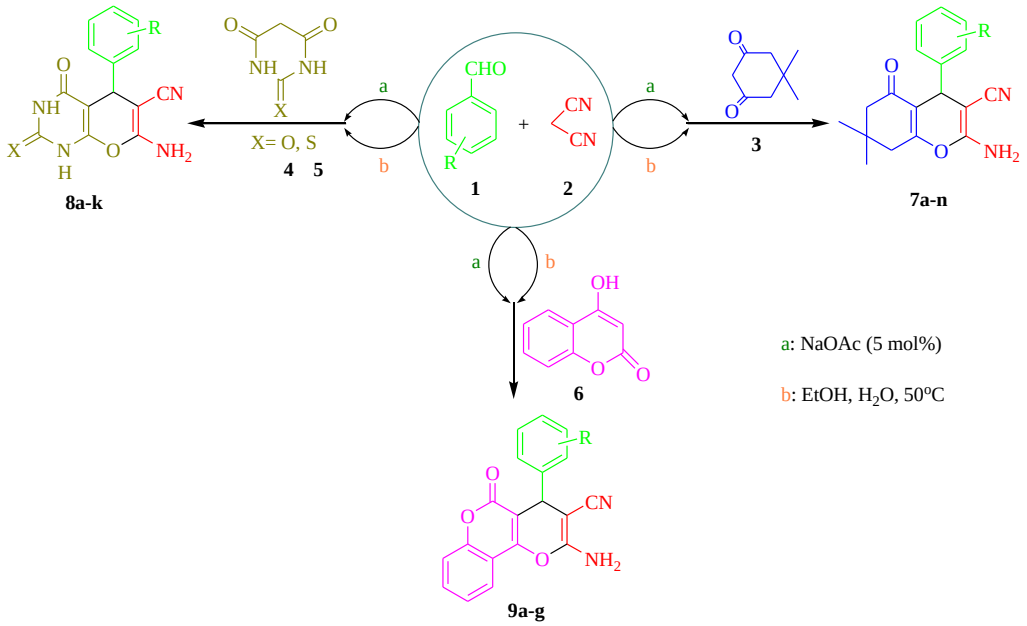
Introduction

Recently, tetrahydrobenzo[*b*]pyran, Pyrano[2,3-d]pyrimidine, and pyrano[*c*]chromene derivatives have attracted much attention due to their wide range of biological properties [1-3]. Pyran[2,3*d*]pyrimidines are annulated uracils which have received considerable attention. Compounds with these ring systems have diverse pharmacological activities such as antitumour [4,5], cardiotonic, hepatoprotactive, antihypertensive [6,7], and antibronchitic [8]. 4H-pyrans and their derivatives have also attracted great attention due to their useful biological and pharmacological properties, such as anticoagulant, spasmolytic, anticancer, and antianaphylactin agents [9]. Some 2-amino-4Hpyrans can be employed as photoactive materials [10]. Furthermore, substituted 4H-pyrans also constitute a structural unit of a series of natural products [11]. A variety of technologies including the use of microwave [12], ultrasonic [13], and catalysis by tetrabutyl ammonium bromide (TBAB) [14], fluoride anion [15], rare earth perfluorooctanoate [16], acidic ionic liquids (ILs) [17], Na_2SeO_4 [18], high surface area MgO [19], [bmim]OH [20], *etc*. were found to be efficient to promote substituted 4H-pyrans. In spite of the merits of these procedures, each of them suffers at least from one of the following limitations: low yields, unavailability of the catalyst, long reaction time. Following our work on MCRs [21-25], we report a general and highly efficient method for the synthesis of tetrahydrobenzopyrans, pyrano[2,3-d]pyrimidine, and 3,4-dihydropyrano[c]chromene derivatives using an inexpensive, clean, safe, environmentally and commercially available sodium acetate catalyst (Scheme **1**). This is a one-pot reaction in aqueous ethanol which is not only operationally simple, clean, and efficient, but also consistently gives corresponding products in excellent yields.

Results and discussion

*Corresponding author. Tel: (+98) 541 2416586, Fax: (+98) 541 2416586, E-mail: mt_maghsoodlou@chem.usb.ac.ir

In order to optimize the conditions, the reaction between benzaldehyde, dimedone, malononitrile, and 10 mol% of sodium acetate as a simple model substrate was undertaken in various conditions. First, we tested the effect of various solvents. It is noteworthy to mention that the polar solvents such as water and ethanol or methanol afford better yields than nonpolar ones, and the mixture of water and ethanol is the most effective solvent (Table **1**, Enties 1-11). In addition, the same model reaction was carried out in water and ethanol at different temperatures to assess the effect of temperature on the reaction yield. It was observed that yield was a function of temperature, since the yield increased as the reaction temperature increased at 50 ^{o}C, the product **7a** was obtained in an excellent yield and higher temperature did not increase the reaction yield (Table **1**, Entries 12-15). The effect of the amount of the catalyst on these reactions was also investigated. As a result, with the mixture of benzaldehyde, malononitrile, and dimedone in the presence of 3 mol% NaOAc, the product **7a** was obtained in 87% yield at 50 ^{o}C in water and ethanol for 20 min. Increasing the amount of catalyst to 5 mol%, 10 mol%, 15 mol%, and 20 mol%, yields of 92%, 92%, 90%, and 88% were obtained, respectively. The use of only 5 mol% NaOAc is sufficient to push the reaction forward, and higher amounts of the catalyst did not improve the results to any greater extent. Thus, 5 mol% was chosen as a suitable amount of catalyst for these reactions (Table **1**, Entries 16-19).



Scheme 1: Synthesis of pyran derivatives using sodium acetate as an effective catalyst.

Table 1: Optimization of solvent, temperature, and catalyst in the synthesis of compound **7a**.

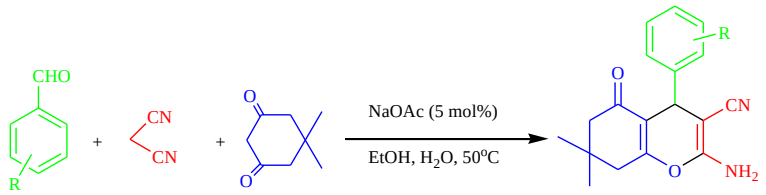
Entry	Solvent/ Temp (°C)	Catalyst (mol%)	Time (min)	Yield (%)[a]
1	CH_2Cl_2/rt	10	110	74
2	THF/rt	10	110	73
3	*n*-Hexan/rt	10	110	72
4	EtOAc/rt	10	90	55
5	H_2O/rt	10	65	74
6	EtOH/rt	10	75	83
7	H_2O. EtOH (1:1)/rt	10	55	84
8	H_2O. EtOH(2:1)/rt	10	50	86
9	H_2O. EtOH(4:1)/rt	10	47	86
10	CH_3CN/rt	10	75	Trace
11	MeOH/rt	10	60	76
12	H_2O. EtOH(4:1)/40	10	22	88
13	H_2O. EtOH(4:1)/50	10	12	92
14	H_2O. EtOH(4:1)/60	10	12	92
15	H_2O. EtOH(4:1)/ 80	10	10	86
16	H_2O. EtOH(4:1)/50	3	20	87
17	H_2O. EtOH(4:1)/50	5	12	92

18	H_2O. EtOH(4:1)/50	15	15	90
19	H_2O. EtOH(4:1)/50	20	15	88

[a] Yield refers to the pure isolated products.

To estimate the generality and versatility of the catalyst, the same reactions were applied for the synthesis of pyrano[2,3-d]pyrimidine and 3,4-dihydropyrano[c]chromene derivatives by replacing dimedone with barbituric acid, thio barbituric acid, and 4-hydroxycoumarin. In each case, the products were obtained in exellent yields. To explor the scope of the procedure, we extended this reaction to various aromatic aldehydes in the presence of electron-withdrawing or electron-releasing substituents, both of which gave the desired product (Tables **2**, **3** and **4**). We observed that the activity of 4-hydroxycoumarin is better than that of thio barbituric acid, the latter being better than barbituric acid, and also this one is more reactive than dimedone.

Table 2: Synthesis of pyran derivatives using sodium acetate.

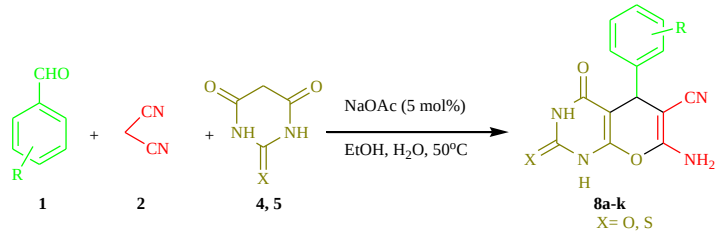


1 **2** **3** **7a-n**

Entry	R	1,3-Dicabonyl	Product	Time (min)	Yield (%)[a]	Mp (°C)	Lit. mp (°C) [Ref]
1	H	3	**7a**	12	92	228-230	228-230 [26]
2	4-Me	3	**7b**	20	89	214-215	212-215 [29]
3	4-Cl	3	**7c**	15	94	209-211	210-212 [27]
4	4-OH	3	**7d**	36	90	201-203	204-206 [28]
5	4-$N(Me)_2$	3	**7e**	40	87	218-219	218-220 [8]
6	2,4-$(Cl)_2$	3	**7f**	9	95	118-120	115-117 [16]
7	3-OH	3	**7g**	12	95	233-234	236-238 [32]
8	2-Cl	3	**7h**	18	97	208-210	208-210 [27]
9	3-Cl	3	**7i**	12	85	234-236	228-229 [30]
10	3-NO_2	3	**7j**	14	98	208-210	208-211 [29]
11	2-NO_2	3	**7k**	14	93	240-242	224-226 [31]
12	4-OH-3-OMe	3	**7l**	32	89	236-238	226-230 [33]
13	2,3-$(OMe)_2$	3	**7m**	35	88	219-220	216-218 [27]
14	3,4-$(OMe)_2$	3	**7n**	12	91	207-209	210-212 [34]

[a] Yields refer to the pure isolated products.

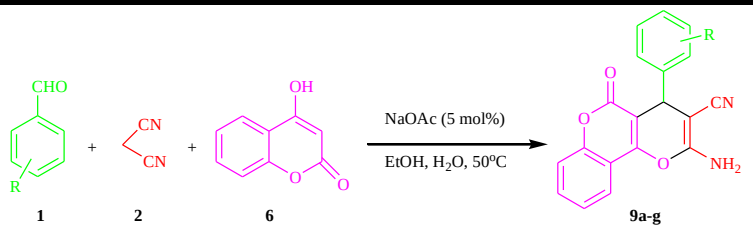
Table 3: Synthesis of pyrano[2,3-d]pyrimidine derivatives using sodium acetate.



Entry	R	1,3-Dicabonyl	Product	Time (min)	Yield (%)[a]	Mp (°C)	Lit. mp (°C) [Ref]
1	H	4	**8a**	7	94	210-211	208-210 [35]
2	4-NO_2	4	**8b**	12	95	236-238	238-239 [35]
3	4-NO_2	5	**8c**	14	98	234-236	235-236 [36]
4	3-NO_2	4	**8d**	4	91	269-271	268-270 [36]
5	3-NO_2	5	**8e**	15	96	234-235	233.5-234 [36]
6	2,4-$(Cl)_2$	4	**8f**	12	88	240-242	241-242 [36]
7	2,4-$(Cl)_2$	5	**8g**	8	95	237-238	238.5-239.5 [36]
8	4-Cl	4	**8h**	7	91	238-240	240-241 [35]
9	3-Cl	4	**8i**	4	93	239-241	240-241 [36]
10	3-Cl	5	**8j**	28	94	236-238	237-238 [36]
11	2-Cl	4	**8k**	13	84	218-220	214-215 [35]

[a] Yields refer to the pure isolated products.

Table 4: Synthesis of 3,4-dihydropyrano[c]chromene derivatives using sodium acetate.



Entry	R	1,3-Dicabonyl	Product	Time (min)	Yield (%)[a]	Mp (°C)	Lit. mp (°C) [Ref]
1	H	6	**9a**	7	94	258-260	255-256 [37]
2	4-Me	6	**9b**	8	92	251-253	254-256 [40]
3	4-Cl	6	**9c**	8	97	258-260	261-262 [37]
4	3-Cl	6	**9d**	6	98	243-245	244-245 [39]
5	2-Cl	6	**9e**	8	96	275-277	273-274 [40]
6	2,4-$(Cl)_2$	6	**9f**	10	96	262-263	261-262 [38]

7	3-NO_2	6	**9g**	5		95	257-259	261-262 [38]

[a] Yields refer to the pure isolated products.

Conclusion

In conclusion, we report a green and novel three-component one-pot synthesis of functionalised tetrahydrobenzo[b]pyran, pyrano[2,3-d]pyrimidine, and 3,4-dihydropyrano[c]chromene derivatives in the presence of NaOAc as a highly effective base catalyst under thermal conditions. There is no doubt that NaOAc is an effective catalyst and provides a new and useful method of synthesizing pyran annulated heterocyclic systems by the condensation of aldehydes, 1,3-dicarbonyl compounds, and malononitrile. The catalyst shows an environmental friendly character which is inexpensive, clean, safe, nontoxic, and easily obtained. Moreover, the procedure offers several advantages including high yields, operational simplicity, clean reaction conditions, and the minimum pollution of the environment, which make it a useful and attractive process for the synthesis of these compounds**.**

Experimental

Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a JASCO FT-IR-460 plus spectrometer, respectively. The ^{1}H NMR spectra were obtained on Bruker DRX- 400 Avance instruments with DMSO and acetone as a solvent. All reagents and solvents were obtained from Fluka and Merck and were used without further purification.

General procedure for the synthesis of pyran derivatives:

A mixture of an appropriate aldehyde (1 mmol), malononitrile (1 mmol), and dimedone/barbituric acid/thio barbituric acid or 4-hydroxycoumarin (1 mmol) in the presence of sodium acetate (5 mol%) in the mixture of water and ethanol(4:1, 5 mL) was heated for aproper period of time. After the completion of the reaction as indicatedby TLC, the reaction mixture was filtrated and the precipitated solid was purified by recrystallization from EtOH 95% to yield the corresponding pyran derivatives in high yields as shown in Table **2**. Physical and spectral data of the products (**7a**, **7b**, **7d**, **7m**, **8d** and **9a**):

*Compound **(7a)***: white solid; Yield: 92%; m.p. 228-230 °C; IR (ν_{max}, cm^{-1}, KBr): 3395, 3323, 3027, 2960, 2199, 1680; ^{1}H-NMR (400 MHz, Acetone-d_6, δ / ppm): 1.04 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.16 (d, J =16.0 HZ, 1H, H-6), 2.28 (d, J =16.0 HZ, 1H, H-6'), 2.58 (s, 2H, CH_2), 4.30 (s, 1H, H-4), 6.25 (brs, 2H, NH_2), 7.19 (m, 1H, H-Ar), 7.28 (m, 4H, H-Ar).

*Compound **(7b)***: white solid; Yield: 89%; m.p. 214-215 °C; IR (ν_{max}, cm^{-1}, KBr): 3465, 3320, 2955, 2190, 1676, 1247; ^{1}H-NMR (400 MHz, $CDCl_3$, δ / ppm): 1.06 (s,3H, CH_3), 1.12 (s,3H, CH_3), 2.23 (dd, J = 21.6, 16.4 Hz, 2H, H-8), 2.30 (s,3H, CH_3), 2.46 (t, J= 19.2 Hz, 2H, H-6), 4.38 (s, 1H, H-4), 4.52 (s, 2H, NH_2), 7.10 (d, J = 8 Hz, 2H, H-Ar), 7.13 (dd, J = 6.0, 2.4 Hz, 2H, H-Ar).

*Compound **(7d)***: white solid; Yield: 90%; m.p. 201-203 °C; IR (ν_{max}, cm^{-1}, KBr): 3285, 3160, 2960, 2185, 1675, 1209; ^{1}H NMR (400 MHz, $CDCl_3$, δ / ppm): 1.05 (s,3H, CH_3), 1.12 (s,3H, CH_3), 2.24 (dd, J= 20.8, 16.4 Hz, 2H, H-8), 2.46 (t, J= 19.2 Hz, 2H, H-6), 4.36 (s, 1H, H-4), 4.53 (s, 2H, NH_2), 5.26 (s, 1H, OH), 6.71-6.74 (m, 2H, H-Ar), 7.08-7.12 (m, 2H, H-Ar).

*Compound **(7m)***: white solid; Yield: 88%; m.p. 219-220 °C; IR (ν_{max}, cm^{-1}, KBr): 3305, 3205, 2945, 2175, 1676, 1212; ^{1}H-NMR (400 MHz, $CDCl_3$, δ / ppm): 1.08 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.21 (dd, J = 21.2, 16.0 Hz, 2H, H-8), 2.39-2.51 (m, 2H, H-6), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.52 (s, 2H, NH_2), 4.74 (s, 1H, H-4), 6.72 (dd, J = 7.8, 1.2 Hz, 1H, H-Ar), 6.79 (dd, J = 8.2, 1.6 Hz, 1H, H-Ar), 6.97 (t, J = 8.0 Hz, 1H, H-Ar).

*Compound **(8d)***: dark yellow solid; Yield: 91%; m.p. 269-271 °C; IR (ν_{max}, cm^{-1}, KBr): 3415, 3311, 3203, 3102, 3022, 2193, 1710; ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 4.48 (s, 1H, CH), 7.30 (s, 2H, NH_2), 7.60 (t, 1H, H-Ar), 7.70 (d, 1H, H-Ar), 8.0 (t, 2H, H-Ar), 11.12 (s, 1H, NH), 12.18(s, 1H, NH).

*Compound **(9a)***: white solid; Yield: 94%; m.p. 258-260 °C; IR (ν_{max}, cm^{-1}, KBr): 3377, 3284, 3255, 3179, 2198, 1708; ^{1}H NMR (400 MHz, Acetone-d_6, δ / ppm): 4.57 (1H, s, CH), 6.70 (2H, brs, NH_2), 7.26-8.0 (9H, m, H-Ar).

Acknowledgments

Financial support from the Research Council of the University of Sistan and Baluchestan is gratefully acknowledged.

References

[1] Andreani, L. L.; Lapi, E. *Bull. Chim. Farm*. **1960**, *99*, 583.
[2] Zhang, Y. L.; Chen, B. Z.; Zheng, K. Q.; Xu, M. L.; Lei, X. H. *Yao. Xue. Xue., Bao*. **1982**, *17(1)*, 17.
[3] Bonsignore, L.; Loy, G.; Secci, D. *Eur. J. Med. Chem*. **1993**, *28*, 517.
[4] Anderson, G. L.; Shim, J. L.; Broom, A. D. *J. Org. Chem*. **1976**, *41*, 1095.
[5] Grivaky, E. M.; Lee, S. C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem.* **1980**, *23*, 327.
[6] Furuya, S.; Ohtaki, T. Eur. Pat. Appl. EP, 608565, 1994; *Chem. Abstr*. **1994**, *121*, 205395w.
[7] Heber, D.; Heers, C.; Ravens, U. *Pharmazie* **1993**, *48*, 537.
[8] Sakuma, Y.; Hasegawa, M.; Kataoka, K.; Hoshina, K.; Yamazaki, N.; Kadota, T.; Yamaguchi, H. PCT Int. Appl. WO 9105785, 1989*; Chem. Abstr*. **1991**, *115*, 71646u.
[9] Loy, L.; Bonsignore, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517.
[10] Armetso, D.; Horspool, W. M.; Martin, N.; Ramos, A.; Seaone, C. *J. Org. Chem.* **1989**, *54*, 3069.
[11] Hatakeyama, S.; Ochi, N.; Numata, H.; Takano, S. *J. Chem. Soc. Chem. Commun*. **1988**, 1202.
[12] Devi, I.; Bhuyan, P. J. *Tetrahedron Lett*. **2004**, *45*, 8625.
[13] Tu, S. J.; Jiang, H.; Zhuang, Q. Y.; Miu, C. B.; Shi, D. Q.; Wang, X. S.; Gao, Y. *Chin. J. Org. Chem*. **2003**, *23*, 488.
[14] Khurana, J. M.; Kumar, S. *Tetrahedron Lett*. **2009**, *50*, 4125.
[15] Gao, S. J.; Tsai, C. H.; Tseng, C.; Yao, C. F. *Tetrahedron* **2008**, *64*, 9143.
[16] Wang, L. M.; Shao, J. H.; Tian, H.; Wang, Y. H.; Liu, B. *J. Fluorine. Chem*. **2006**, *127*, 97.
[17] Fang, D.; Zhang, H. B.; Liu, Z. L. *J. Heterocycl. Chem*. **2010**, *47*, 63.
[18] Hekmatshoar, R.; Majedi, S.; Bakhtiari, K. *Catal. Commun*. **2008**, *9*, 307.
[19] Seifi, M.; Sheibani, H. *Catal. Lett.* **2008**, *126*, 275.
[20] Gong, K.; Wang, H. L.; Luo, J.; Liu, Z. L. *J. Heterocycl. Chem.* **2009**, *46*, 1145.
[21] Mousavi, M. R.; Hazeri, N.; Maghsoodlou, M. T.; Salahi, S.; Habibi-Khorassani, S. M. *Chin. Chem. Lett*. **2013**, *24*, 411.
[22] Hazeri, N.; Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Aboonajmi, J.; Lashkari, M.; Sajadikhah, S. S. *Res. Chem. Intermed*. **2014**, *40*, 1781.
[23] Aboonajmi, J.; Mousavi, M. R.; Maghsoodlou, M. T.; Hazeri, N.; Masoumnia, A. *Res. Chem. Intermed*. **2013**, DOI: 10.1007/s11164-013-1320-z.
[24] Mousavi, M. R.; Aboonajmi, J.; Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Safarzaei, M. *Lett. Org. Chem*. **2013**, *10*, 171.
[25] Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Moradi, A.; Hazeri, N.; Davodi, A.; Sajadikhah, S. S. *Tetrahedron* **2011**, *67*, 8492.
[26] Ranu, B. C.; Banerjee, S. *Ind. J. Chem. Soc*. **2008**, *47*, 1108.
[27] Gurumurthi, S.; Sundari, V.; Valliappan, R. *E.-J. Chem*. **2009**, *6*, s466.
[28] Yu, L. Q.; Liu, F.; You, Q. D. *Org. Prep. Proced. Int*. **2009**, *41*, 77.
[29] Kumar, D.; Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. *Eur. J. Med. Chem*. **2009**, *44*, 3805.
[30] Balalaie, S.; Shiekh-Ahmadi, M.; Barazjanian, M. *Cat. Commun*. **2007**, *8*, 1724.
[31] Jin, T. S.; Wang, A. Q.; Wang, X.; Zhang, J. S.; Li, T. S. *Synlett* **2004**, 0871.
[32] Balalaie, S.; Bararjanian, M.; Amani, A. M.; Movassagh, B. *Synlett* **2006**, 263.
[33] Tu, S.; Gao, Y.; Guo, C.; Shi, D.; Lu, Z. *Synth Commun*. **2002**, *32*, 2137.
[34] Wang, X. S.; Shi, D. Q.; Tu, S. J.; Yao, C. S. *Synth. Commun*. **2003**, *33*, 119.
[35] Sharanin, Y. A.; Klokol, G. V. *Zh. Org. Khim*. **1984**, *20*, 2448.
[36] Bararjanian, M.; Balalaie, S.; Movassagh, B.; Amani, A. M.; *J. Iran. Chem. Soc*. **2009**, *6*, 436.
[37] Kidwai, M.; Saxena, S. *Synth. Commun*. **2006**, *36*, 2737.
[38] Heravi, M. M.; Alimadadi, J. B.; Derikvand, F.; Bamoharram, F. F.; Oskooei, H. A. *Catal. Commun*. **2008**, *10*, 272.
[39] Xiang-Shan, W.; Zhao-sen, Z.; Da-Qing, S.; Xian-Yong, W.; Zhi-Min, Z. *Chin. J. Org. Chem*. **2005**, *25*, 1138.
[40] Da-Qing, S.; Jing, W.; Qi-Ya, Z.; Xiang-Shan, W. *Chin. J. Org. Chem*. **2006**, *26*, 643.