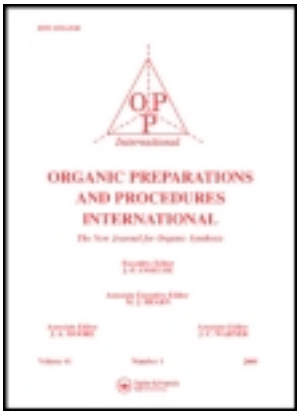

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An Expedient Synthesis of β-Acetamido- and β-Benzamidocarbonyl Compounds via $KAl(SO_4)_2 \cdot 12H_2O$-catalyzed Three-component Coupling Reaction

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An Expedient Synthesis of β-Acetamido- and β-Benzamidocarbonyl Compounds *via* $KAl(SO_4)_2 \cdot 12H_2O$-catalyzed Three-component Coupling Reaction

Aniruddha Molla and Sahid Hussain

Department of Chemistry, Indian Institute of Technology Patna, Patna 800 013, India

β-Aminocarbonyl compounds are important structural units of several biologically active compounds such as *dolastins, astins, onchidin, jasplakinolide and motuporin*,[1] and useful building blocks for β-lactams[2,3] and β-peptides[4] that are present in a variety of drugs.[5] Traditionally, this class of compounds is prepared by the Dakin-West reaction;[6–8] the condensation of α-amino acids with acetic anhydride in the presence of a base provides the α-acetamidoketones through intermediate azalactones. In recent years, the Mannich reaction[9,10] and its variants have been used in the synthesis of several biologically and pharmacologically important β-aminocarbonyl compounds.[5] One of the interesting ways for the synthesis of β-aminocarbonyl compounds is multi-component coupling of aldehyde, enolizable ketone, acetyl chloride and acetonitrile first reported by Iqbal and coworkers[11–13] and later by some other groups using catalyst such as Bi-salts,[14] zeolite Hβ,[15] $Zn(OTf)_2$,[16] $Cu(OTf)_2$ and $Sc(OTf)_3$,[17] $ZrOCl_2 \cdot 8H_2O$,[18,19] $CeCl_3 \cdot 7H_2O$,[20] chiral Brönsted acid,[21] sulfamic acid[22], cellulose-H_2SO_4,[23] SiO_2-H_2SO_4,[24] TMSCl,[25] $FeCl_3$,[26] hetaropoly acid,[27] $Zn(HSO_4)_2$,[28] and silica-supported perchloric Acid.[29] Though the reported methods are worthy, they suffer from some drawbacks such as requiring air-sensitive or costly catalysts[14–21] and harsh reaction conditions (high temperatures).[23–25] Therefore, the elaboration of new methods for this type of multi-component reaction is still useful. In continuation of our investigations the synthesis of β-aminocarbonyl compounds,[30–32] we were prompted to explore the use of aluminium potassium sulfate dodecahydrate ($KAl(SO_4)_2 \cdot 12H_2O$)[33,34] a naturally occurring material, widely available, water-soluble, air-stable, relatively nontoxic and inexpensive reagent able to activate the carbonyl group. Herein, we report an efficient and convenient procedure for the synthesis of β-aminocarbonyl compounds using $KAl(SO_4)_2 \cdot 12H_2O$ as a catalyst (*Scheme 1*).

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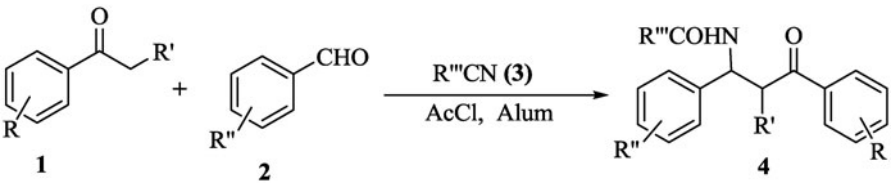
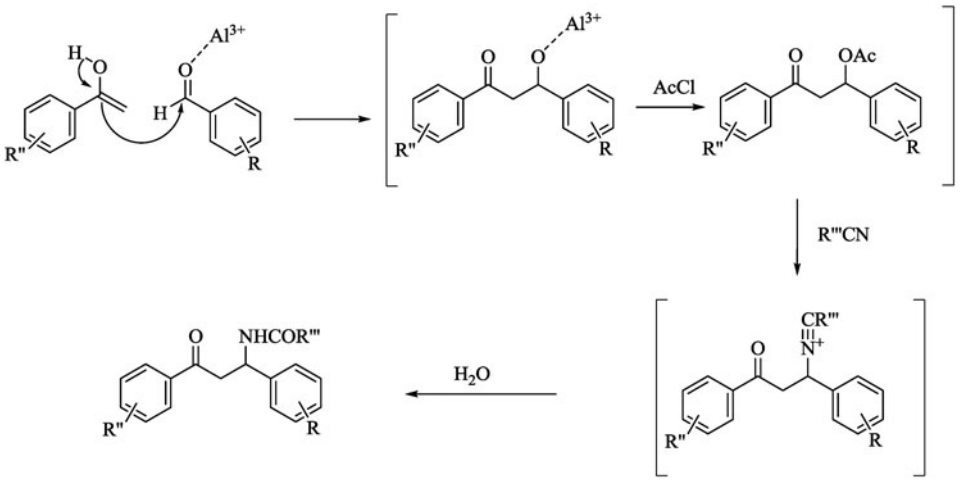


Scheme 1
$KAl(SO_4)_2 \cdot 12H_2O$ catalyzed synthesis of β-aminocarbonyl compounds.

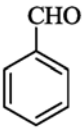
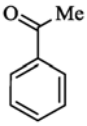
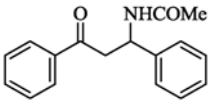
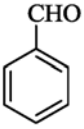
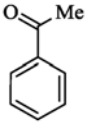
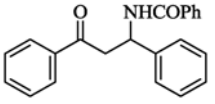
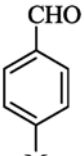
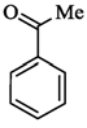
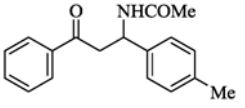
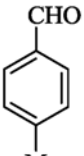
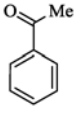
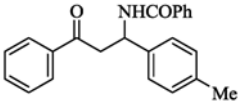
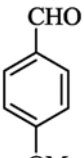
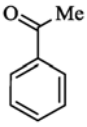
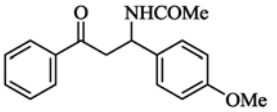
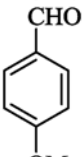
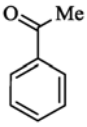
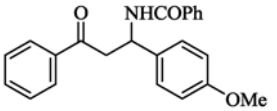
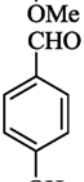
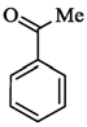
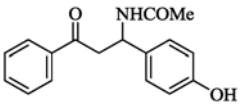
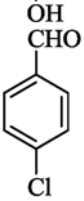
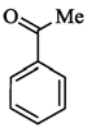
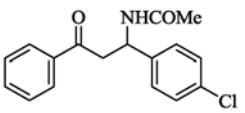
In order to determine the optimal reaction conditions, several experiments were carried out with a mixture of benzaldehyde (2 mmol), acetophenone (2 mmol), acetyl chloride (3 mmol) and acetonitrile (3 ml) at room temperature. In the absence of the catalyst, the expected product was obtained in only 15% yield and after 24 h; a longer time was required with 1 and 5 mol% of catalyst. However, since the use of 10 mol% catalyst furnished the β-acetamidocarbonyl compounds in good yields, all the reactions were conducted with this catalyst ratio (based on benzaldehyde). No product was formed in the absence of acetonitrile and of acetyl chloride.

A variety of electron-donating and electron-withdrawing substituted aromatic aldehydes underwent the reaction smoothly giving the desired products in good yields (*Table 1)*. Aromatic aldehydes bearing a nitro substituent required longer reaction times (*Entries 12–16*). In order to confirm product formation, the crystal structure of the product in *Entry 14* was obtained. CCDC-874016 contains the supplementary crystallographic data. Reactions carried out with benzonitirile instead of acetonitrile proceed to furnish β-benzamidoketones in good yields. The likely mechanistic pathway is proposed for this reaction (*Scheme 2*).



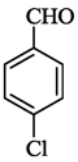
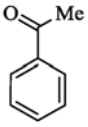
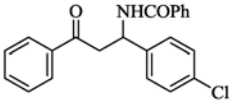
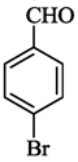
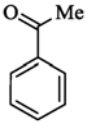
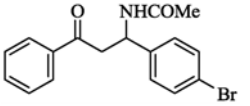
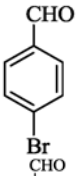
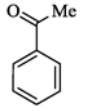
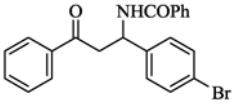
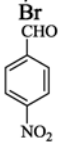
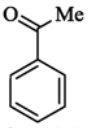
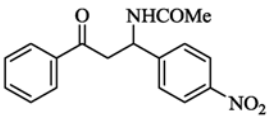
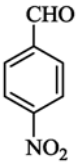
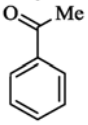
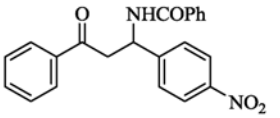
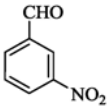
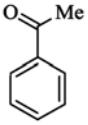
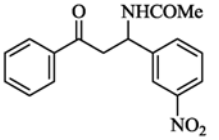
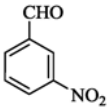
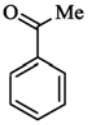
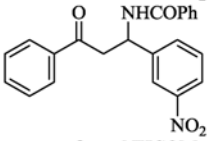
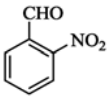
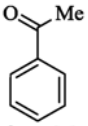
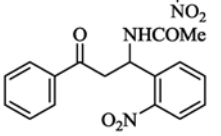
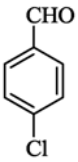
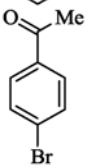
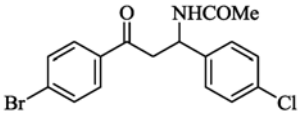
Scheme 2
Probable mechanism of alum catalyzed reaction for the preparations of β-acetamidocarbonyl compounds.

Table 1
$KAl(SO_4)_2 \cdot 12H_2O$-catalyzed Condensations

Entry	Aldehyde	Ketone	Products	Time (h)	Yield (%)	mp (°C)
01				8	88	100 (102–104[26])
02				8	91	150 (153–154[26])
03				10	83	110 (113–115[25])
04				10	81	170 (172–173[27])
05				10	84	105 (110–111[26])
06				10	78	170 (172–174[27])
07				10	83	120 (120–122[28])
08				10	96	145 (146–148[26])

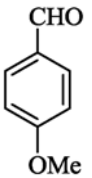
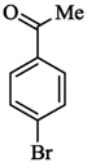
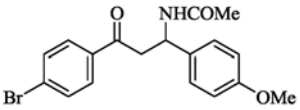
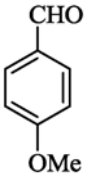
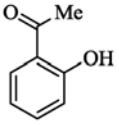
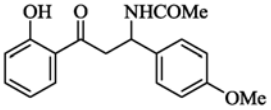
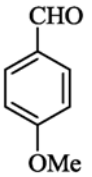
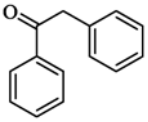
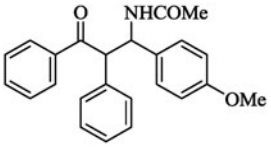
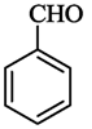
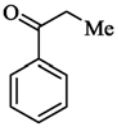
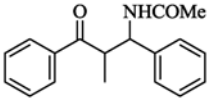
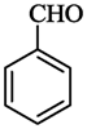
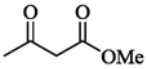
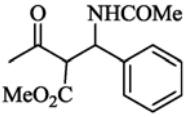
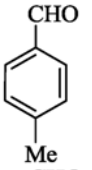
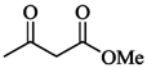
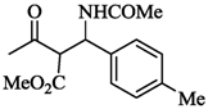
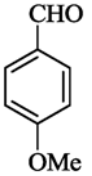
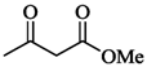
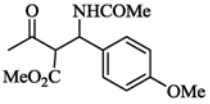
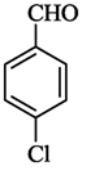
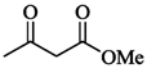
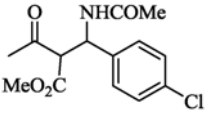
(Continued on next page)

Table 1
$KAl(SO_4)_2 \cdot 12H_2O$-catalyzed Condensations
(Continued)

Entry	Aldehyde	Ketone	Products	Time (h)	Yield (%)	mp (°C)
09				11	91	180 (180–182[26])
10				10	97	144 (148–150[26])
11				11	90	170 (see *Table 2*)
12				12	88	150 (153–154[26])
13				13	82	140 (142–144[26])
14				13	86	140 (139–140[26])
15				13	84	200 (199–200[18])
16				13	85	186 (186–188[26])
17				9	78	125 (125–127[29])

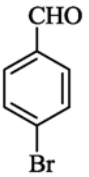
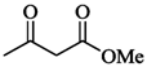
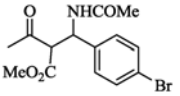
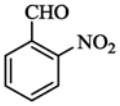
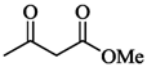
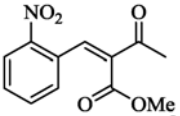
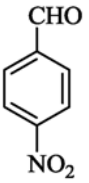
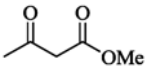
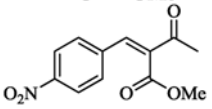
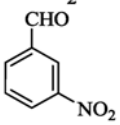
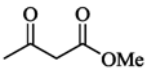
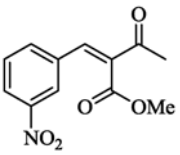
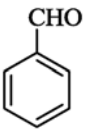
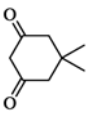
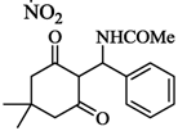
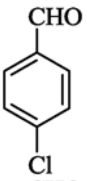
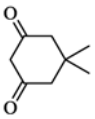
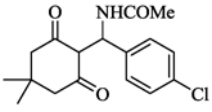
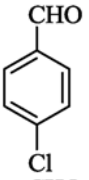
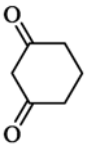
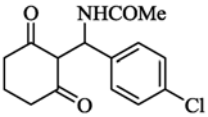
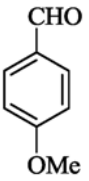
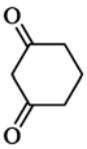
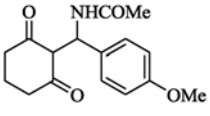
(Continued on next page)

Table 1
$KAl(SO_4)_2 \cdot 12H_2O$-catalyzed Condensations
(Continued)

Entry	Aldehyde	Ketone	Products	Time (h)	Yield (%)	mp (°C)
18				10	79	135 (see *Table 2*)
19				12	80	137–139 (see *Table 2*)
20				15	77	100–102 (see *Table 2*)
21				15	76	108–110 (see *Table 2*)
22			 21:79[a]	14	80	131 (128–130[26])
23			 25:75[a]	14	74	130 (130[19])
24			 47:53[a]	14	79	140 (140–143[26])
25			 29:71[a]	14	76	130 (131–133[26])

(Continued on next page)

Table 1
$KAl(SO_4)_2 \cdot 12H_2O$-catalyzed Condensations
(Continued)

Entry	Aldehyde	Ketone	Products	Time (h)	Yield (%)	mp (°C)
26			 28:72[a]	14	75	145 (146[19])
27				10	71	98 (90–93[26])
28				10	74	110 (110–114[26])
29				10	76	150 (151–152[26])
30				3.0	82	198 (200[23])
31				3.5	85	196 (195[23])
32				3.5	80	185 (see *Table 2*)
33				4.0	79	170 (see *Table 2*)

[a]syn:anti ratio.

Table 2
Spectroscopic data of New Compounds (from *Table 1*)

Cmpd[a]	IR (cm^{-1})	^{1}H-NMR (δ) ($CDCl_3$)	^{13}C-NMR (δ) ($CDCl_3$+DMSO-d_6)	Combustion Analysis (Found)		
				C	H	N
11[b]	3276, 3069, 2945, 1682, 1643, 1541,	7.82 - 7.93 (4H, m), 7.71 (1H, d, J = 7.8 Hz), 7.42–7.61 (8H, m), 7.26–7.30 (2H, m), 5.69–5.75 (1H, m), 3.85 (1H, dd, J = 4.8, 17.1 Hz), 3.52 (1H, dd, J = 5.7, 17.1 Hz),		64.72 (64.89)	4.44 (4.50)	3.43 (3.48)
18[b]	3298, 3007, 1689, 1654, 1585	7.78 (2H, d, J = 8.4 Hz), 7.58 (2H, d, J = 8.4 Hz), 7.23 (2H, d, J = 8.8 Hz), 6.83 (2H, d, J = 8.4 Hz), 6.47 (1H, d, J = 7.2 Hz), 5.45–5.50 (1H, m), 3.76 (3H, s), 3.72 (1H, dd, J = 5.2, 16.8 Hz), 3.36 (1H, dd, J = 6.8, 19.2 Hz), 2.01 (3H, s)	197.6, 169.5, 158.9, 135.3, 132.6, 132.0, 129.7, 128.8, 127.8, 114.1, 55.3, 49.7, 43.4, 23.5	57.46 (57.30)	4.82 (5.01)	3.72 (3.80)
19[b]	3270, 3099, 1646, 1525	12.26 (1H, s), 7.80–7.82 (1H, m), 7.44–7.48 (1H, m), 7.22–7.25 (2H, m), 6.91–6.98 (2H, m), 6.82–6.88 (1H, m), 6.38 (1H, d, J = 7.2 Hz), 5.45 (1H, dd, J = 6.8, 12.8 Hz), 3.77 (3H, s), 3.73–3.75 (1H, m), 3.39–3.45 (1H, m), 1.99 (3H, s).	204.1, 169.5, 162.5, 159.0, 136.8, 132.4, 130.1, 127.8, 119.4, 119.2, 118.6, 114.1, 55.2, 49.8, 43.2, 23.4	68.99 (68.81)	6.11 (6.20)	4.47 (4.52)
20[c]	3256, 3078, 1689, 1518	9.88 (3H, s), 8.00–8.02 (2H, m), 7.51–7.87 (3H, m), 7.27–7.47 (5H, m), 6.70–6.79 (4H, m), 5.32–5.88 (2H, m), 3.70 (3H, s), 2.06 (3H, s).	197.3, 159.0, 136.3, 135.7, 133.5, 131.9, 129.4, 129.0, 128.9, 128.7 (2C), 128.3, 127.9, 113.8, 57.7, 56.9, 55.2, 22.2.	77.19 (77.20)	6.21 (6.39)	3.75 (3.81)

Table 2
Spectroscopic data of New Compounds (from *Table 1*) *(Continued)*

Cmpd[a]	IR (cm^{-1})	^{1}H-NMR (δ) ($CDCl_3$)	^{13}C-NMR (δ) ($CDCl_3$+DMSO-d_6)	Combustion Analysis (Found) C	H	N
21[c]	3312, 2972, 1688, 1653, 1554	8.41 (1H, t, J = 8.8 Hz), 8.02 (1H, d, J = 7.6 Hz), 7.78 (1H, d, J = 7.6 Hz), 7.08–7.63 (7H, m), 5.16–5.27 (1H, m), 4.88 (1H, brs), 4.01–4.10 (1H, m), 1.94 (3H, s), 1.19 (3H, d, J = 6.8 Hz).	201.7, 168.4, 140.9, 136.2, 133.8, 128.2, 127.9, 127.8, 127.6, 127.3, 54.9, 45.1, 22.4, 15.4	76.84 (76.91)	6.81 (6.89)	4.98 (4.92)
32[c]	3356, 2952, 1616, 1491	11.22 (1H, s), 8.22 (1H, d, J = 6.4 Hz), 7.18–7.26 (4H, m), 6.31 (1H, d, J = 7.6 Hz), 2.52 (2H, m), 2.31 (2H, m), 2.07 (3H, s), 1.91 (2H, m).	195.9, 168.6, 141.1, 128.5, 127.5, 115.5, 45.8, 36.4, 30.7, 26.3, 20.2	61.33 (61.26)	5.49 (5.68)	4.77 (4.82)
33[c]	3356, 2954, 1617, 1512	11.21 (1H, s), 8.15 (1H, d, J = 6.0 Hz), 7.25 (2H, d, J = 7.6 Hz), 6.78 (2H, d, J = 7.2 Hz), 6.31 (1H, d, J = 7.6 Hz), 2.56 (2H, m), 2.32 (2H, m), 2.05 (3H, s), 1.92 (2H, m).	195.7, 169.3, 157.8, 134.4, 126.8, 112.6, 55.6, 45.7, 37.1, 29.6, 22.9, 20.2	66.42 (66.44)	6.62 (6.75)	4.84 (4.91)

[a]Refers to entry number of *Table 1*. [b]Light yellow solid. [c]White solid.

To extend the scope of the condensation, a variety of aromatic aldehydes (*Entries 22–26*) were treated with methyl acetoacetate and acetyl chloride in the presence of 10 mol% of catalyst at room temperature and the corresponding β-acetamidoketo esters were obtained in good yields and moderate-to-good diastereoselectivities. The reaction with (*ortho, meta, para*) NO_2-substituted aldehydes with methyl acetoacetates gave only Knoevenagel condensation products instead of the expected product (*Entries 27–29*). Treatment of aromatic aldehydes (*Entries 30–33*) with cyclic 1,3-diketones under the same conditions proceeded quite rapidly to give the products in good yields whereas the reactions with aliphatic non-cyclic ketones did not work.

In conclusion, we have developed a simple, efficient and 'greener' protocol for the preparation of β-acetamido- and β-benzamidocarbonyl compounds using alum as relatively non-toxic and inexpensive catalyst. The salient features of this protocol include

operational simplicity, high yields of the products, avoidance of column chromatography, ready availability, relatively low toxicity, and moisture compatibility of the catalyst.

Experimental Section

All reagents were purchased either from Sigma or Merck. Solvents were dried and purified using standard techniques. Melting points were determined on a SRS-EZ-Melt melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Shimadzu IR Afinity I. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained on a Bruker 300 MHz, 500 MHz and Jeol 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as an internal reference and chemicals shifts are in δ (ppm). GC-MS data were determined in Thermo Scientific ITQ 1100 spectrometer. The crystal structure data were acquired using Bruker SMART APEX-II CCD difractometer. CCDC-874016 contains the supplementary crystallographic data for this paper. The data can be extracted free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Preparation of β-Acetamido- and β-Benzamidoketones or β-Keto Esters

To a stirred solution of aldehyde (2 mmol, 0.212 g) and acetophenone (2 mmol, 0.24 g) or methyl acetoacetate (2 mmol, 0.232 g) in acetonitrile (3 ml) [or benzonitrile (3 ml)] were added acetyl chloride (3 mmol, 0.236 g) and $KAl(SO_4)_2 \cdot 12H_2O$ (0.2 mmol, 0.094 g) at room temperature for the time noted in the *Table 1*. After completion of the reaction (monitored by TLC using silica and ethyl acetate-hexane as solvent), crushed ice was added to the reaction mixture which was stirred thoroughly. The solids formed were collected and dried to give the corresponding products which were recrystallized from ethyl acetate-hexane and fully characterized by recording IR, NMR and other analysis.

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References

1. G. Cardillo and C. Tomasini, *Chem. Soc. Rev.*, **25**, 117 (1996).
2. F. H. van der Steen and G. van Koten, *Tetrahedron*, **47**, 7503 (1991).
3. D. J. Hart and D. C. Ha, *Chem. Rev.*, **89**, 1447 (1989).
4. S. Krauthauser, L. A. Christianson, D. R. Powell and S. H. Gellman, *J. Am. Chem. Soc.*, **119**, 11719 (1997).
5. S. B. Rosenblum, T. Huynh, A. Afonso, H. R. Davis Jr., N. Yumibe, J. W. Clader and A. D Burnett, *J. Med. Chem.*, **41**, 973 (1998).
6. M. Arned, B. Westermann and N. Risch, *Angew. Chem. Int. Ed.*, **37**, 1044 (1998).

7. S. Kobayashi and H. Ishitani, *Chem. Rev.*, **99**, 1069 (1999).
8. C. Mannich and W. Krosche, *Arch. Pharm*, **250**, 647 (1912).
9. J. R. Casimir, C. Turetta, L. Ettouati and J. Paris, *Tetrahedron Lett*., **36**, 4797 (1995).
10. A. G. Godfrey, D. A. Brooks, L. A. Hay, M. Peters, J. R. McCarthy and D. Mitchell, *J. Org. Chem*., **68**, 2623 (2003).
11. M. Mukhopadhyay, B. Bhatia and J. Iqbal, *Tetrahedron Lett*., **38**, 1083 (1997).
12. B. Bhatia, M. M. Reddy and J. Iqbal, *J. Chem. Soc. Chem. Commun*., 713 (**1994**).
13. D. Bahulayan, K. S. Das and J. Iqbal, *J. Org. Chem*., **68**, 5735 (2003).
14. R. Ghosh, S. Maity and A. Chakraborty, *Synlett*, 115 (**2005**).
15. R. P. Bhat, V. P. Raje, V. M. Alexander, S. B. Patil and S.D. Samant, *Tetrahedron Lett*., **46**, 4801 (2005).
16. W. G. Shou, Y. Y. Yang and Y. G. Wang, *Tetrahedron Lett*., **47**, 1845 (2006).
17. G. Pandey, R. P. Singh, A. Garg and V. K. Singh, *Tetrahedron Lett*., **46**, 2137 (2005).
18. R. Ghosh, S. Maiti, A. Chakraborty, S. Chakraborty and A. K. Mukherjee, *Tetrahedron*, **62**, 4059 (2006).
19. R. Ghosh, S. Maiti, S. K. Maity and S. Roy, *Synth. Commun*., **38**, 1958 (2008).
20. A. T. Khan, L. H. Choudhury, T. Parvin and M. A. Ali, *Tetrahedron Lett*., **47**, 8137 (2006).
21. M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem. Int. Ed*., **45**, 2254 (2006).
22. M. M. Heravi, L. Ranjbar, F. Derikvand and F. F. Bamoharram, *J. Mol. Catal. A: Chem*., **276**, 226 (2007).
23. H. A. Oskooie, M. M. Heravi, L. Tahershamsi, S. Sadjadi and M. Tajbakshsh, *Synth. Comm*., **40**, 1772 (2010).
24. M. M. Khodaei, A. R. Khosropour and P. Fattahpour, *Tetrahedron Lett*., **46**, 2105 (2005).
25. H. Mao, J. Wan and Y. Pan, *Tetrahedron*, **65**, 1026 (2009).
26. A. T. Khan, T. Parvin and L. H. Choudhury, *Tetrahedron*, **63**, 5593 (2007).
27. M. Lei, L. Ma and L. Hu, *Tetrahedron Lett*., **51**, 4746 (2010).
28. H. R. Shaterian and A. Hosseinian, *Chin. J. Chem*., **27**, 1947 (2009) DOI:10.1002/cjoc. 200990327.
29. M. N. Esfahani, M. Montazerozohori and T. Gholampour, *Chin. J. Chem*., **29**, 123 (2011) DOI:10.1002/cjoc.201190038.
30. S. Hussain, S. K. Bharadwaj, M. K. Chaudhuri and H. Kalita, *Eur. J. Org. Chem*., 374, (2007).
31. M. K. Chaudhuri, S. Hussain, M. L. Kantam and B. Neelima, *Tetrahedron Lett*., **46**, 8329 (2005).
32. M. L. Kantam, V. Neeraja, B. Kavita, B. Neelima, M. K. Chaudhuri and S. Hussain, *Adv. Synth. Catal*., **347**, 763 (2005).
33. A. A. Mohammadi, M. Dabiri and H. Qaraat, *Tetrahedron*, **65**, 3804 (2009).
34. J. Azizian, A. A. Mohammadi, A. R. Karimi and M. R. Mohammadizadeh, *J. Org. Chem*., **70**, 350 (2005).