Pergamon

Tetrahedron Letters 43 (2002) 4261–4265

TETRAHEDRON LETTERS

Ac_2O–Py/basic alumina as a versatile reagent for acetylations in solvent-free conditions under microwave irradiation

Satya Paul,[a] Puja Nanda,[a] Rajive Gupta[a,*] and André Loupy[b]

[a]*Department of Chemistry, University of Jammu, Jammu 180 006, India*
[b]*Laboratoire des Réactions Sélectives sur Supports, CNRS UMR 8615, Université Paris-Sud, 91405 Orsay Cedex, France*

Received 12 February 2002; accepted 11 April 2002

Abstract—Acetic anhydride–pyridine over basic alumina has been used in order to carry out acetylations of hydroxy, thiol and amino groups in solvent-free conditions under microwave irradiation. The technique can be extended for selective acetylations by regulation of irradiation time. © 2002 Elsevier Science Ltd. All rights reserved.

Acetylation is among the most important reactions finding applications in both the laboratory as well as in industry. The most common and cheap reagent used in order to carry out acetylation is acetic anhydride.[1] Pyridine and 4-dialkylaminopyridine are the most commonly used basic catalysts.[2] A variety of either basic or acidic new catalysts have been recently reported. Amongst the basic ones, Bu_3P,[3] $MgBr_2$–R_3N,[4] an aminophosphine superbase[5] and KF–Al_2O_3[6] are the most significant whereas $CoCl_2$,[7] $Sc(OTf)_3$,[8] $Sc(NTf_2)_3$,[9] $TiCl_4$–$2AgClO_4$,[10] $TiCl(OTf)_3$,[11] $Sn(OTf)_2$,[12] $Cu(OTf)_2$[13] and montmorillonite K-10[14] represent the acidic catalysts. *Pseudomonas cepacia* PS lipase[15] and twisted amides[16] have been used for the chemoselective acetylation of aliphatic alcohols present in hydroxy alkyl phenols. The direct acetylation of primary, secondary alcohols and phenols, with no apparent discrimination, using zeolites HSZ-360[17] is also efficient. All these reagents and catalysts lead to wastes as well as some reactions involving solvents, often toxic and polluting, hence unacceptable in these environmentally conscious days.

Since the early articles of Gedye[18] and Giguere,[19] applications of microwave heating techniques have been currently under intensive investigation and were recently reviewed.[20] The effects usually observed are decreases in reaction times, and improvements in yields and purity of final products with easier work-up. Especially interesting was the coupling with dry media conditions[20] which allowed reaction on a preparative scale under atmospheric pressure (avoiding the risk of high pressures and explosions, resulting from reactions carried out in closed vessels). Some microwave-mediated solvent-free acetylations were described using acetic anhydride and various catalysts involving iodine or montmorillonite K-10.[21]

Considering the importance of acetylation in laboratory and industry as well as our interest[22] in devising solvent-free procedures, we report therein acetylations of hydroxy, thiol and amino groups using Ac_2O–Py/basic alumina in solvent-free conditions under microwave irradiation.[23]

Acetic acid, when adsorbed over silica gel, is found to act as a good acetylating agent for aliphatic amines, but fails to give satisfactory results for phenols, thiols, aromatic amines and amino heterocycles. Further, acetic acid and acetic anhydride over different solid supports in the presence of various catalysts have been used to obtain selectively the mono- and diacetates of hydrazine hydrate, in order to select the most efficient one. The results are summarized in Table 1.

From these results, it is obvious that Ac_2O–Py/basic alumina is the most efficient and adaptable reagent as it can be used for the selective acetylation of hydrazine hydrate. Furthermore, the support can be recycled several times without loss of activity. Thus, we have decided to carry out acetylations of aliphatic and aromatic amines, amino heterocycles, phenols and thiols with Ac_2O–Py/basic alumina (Table 2).

Keywords: acetylations; solvent-free conditions; acetic anhydride–pyridine/basic alumina; microwave activation; non-thermal effect.

* Corresponding author. Fax: 91-191-505086; e-mail: rajgupta5@rediffmail.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00732-3

Table 1. Mono- and di-acetylation of hydrazine hydrate according to different supported reagents (power = 300 W)

Reagent	Time (min)	Yield (%)[a]	
		$AcNHNH_2$	AcNHNHAc
$AcOH/SiO_2$	0.25	**100**	0
	12	0	**100**
AcOH/K-10	8	20	80
AcOH/*p*-TsOH/SiO_2	4	30	70
	8	10	90
AcOH/acidic Al_2O_3	8	40	60
AcOH/TFA/SiO_2	8	50	50
AcOH/H_2SO_4/SiO_2	2	**100**	0
Ac_2O/DMSO/SiO_2	6	10	90
AcOH/DMSO/SiO_2	6	0	0
Ac_2O–Py/Basic Al_2O_3	1	100	0
	5	0	**100**
Ac_2O/SiO_2	5	0	0

[a] Yield of isolated products.

The method is environmentally friendly, as acetic acid (by-product) remains adsorbed over the basic alumina and there is no evaporation into the atmosphere. The method can be used for the selective mono- and diacetylations only by regulating the irradiation time (entries 19, 20; 28, 29; 30, 31; 38, 39; 41–44).

In order to operate in an eco-friendly way, we have carried out the acetylation of aniline under different conditions. After several experiments testing molar ratios and amounts of support, we found that for 1 mmole of the reagent, 2 mmoles of Ac_2O and 0.6 mmole of pyridine gave optimum results. The amount of support was also found to be crucial in order to carry out the reaction in Green Chemistry conditions and it has been found that for 1 mmole of the reagent, 2 g of the support were required.

Further, the reaction has been carried out at different power levels ranging from 80 to 800 W for aniline and 2-nitroaniline in order to select the most appropriate power level (300 W). The results are shown graphically in Fig. 1.

Finally, the acetylations of 2-, 3- and 4-nitroanilines were carried out using a thermostated oil-bath under the same conditions of time and temperature as for microwave-assisted method (Table 3).

It has been found that significantly lower yields were obtained using oil-bath heating rather than the microwave-assisted method under identical conditions of reaction and temperature. This observation demonstrates clearly that the effect of microwave irradiation is not purely thermal. These specific MW effects might originate in the rate-determining step of the mechanism (nucleophilic attack of the amine nitrogen lone pair on carbonyl moiety) since it leads to a development of charges in the transition state thus inducing an important exaltation in dipole–dipole interactions (Scheme 1). In this circumstance, an increased stabilization of the dipolar transition state results under MW irradiation when compared with its less polar ground state,[24] and the activation energy is consequently reduced.

In conclusion, we have developed a rapid, safe and eco-friendly method for N-, O- and S-acetylations using Ac_2O–Py over basic alumina under microwave irradiation. The method is inexpensive and the support can be reused several times after washing and drying.

General procedure

To a mixture of substrate (2 mmole), acetic anhydride (4 mmole), pyridine (0.6 mmole), 4 g of basic alumina were added in a beaker (50 mL). The mixture was stirred for 30 s until a free flowing powder was obtained. The reaction mixture (monitored by TLC) was then irradiated in a microwave oven for an appropriate time (Table 2) at 300 W. After cooling down to room temperature, the product was extracted with methylene chloride (3×15 mL). The combined organic extracts were washed with water and dried over sodium sulfate. The product, obtained after removal of the solvent under reduced pressure, was crystallized from an appropriate solvent.

The structures of the products were confirmed by ^1H NMR, IR and comparison with an authentic sample prepared by reported methods. ^1H NMR spectra were recorded using a JNM-PMX 60 NMR spectrometer (60 MHz) and IR spectra by using KBr discs on a Hitachi 270-30 spectrophotometer.

The spectral data of entry 2, 33–44

Entry 2. IR cm^{-1} (KBr): 1707 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.27 (s, 6H, 2×$COCH_3$). **Entry 33**. IR cm^{-1} (KBr): 1586 (C=N), 1720 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.24 (s, 3H, $COCH_3$), 7.66–7.80 (m, 6H, H_{arom}). **Entry 34**. IR cm^{-1} (KBr): 1576 (C=N), 1725 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H, $ArCH_3$), 2.40 (s, 3H, $COCH_3$), 7.66–7.80 (m, 5H, H_{arom}). **Entry 35**. IR cm^{-1} (KBr): 1582 (C=N), 1720 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H, $COCH_3$), 4.36 (bs, 1H, NH, exchangeable with D_2O), 7.26–8.1 (m, 5H, H_{arom}). **Entry 36**. IR cm^{-1} (KBr): 1590 (C=N), 1722 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H, $COCH_3$), 4.35 (bs, 1H, N, exchangeable with D_2O), 7.06–8.0 (m, 5H, H_{arom}). **Entry 37**. IR cm^{-1} (KBr): 1596 (C=N), 1730 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.23 (s, 3H, $COCH_3$), 4.43 (bs, 1H, NH, exchangeable with D_2O), 6.9–7.23 (m, 5H, H_{arom}). **Entry 38**. IR cm^{-1} (KBr): 1576 (C=N), 1725 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H, $COCH_3$), 7.16–7.96 (m, 5H, H_{arom}). **Entry 39**. IR cm^{-1} (KBr): 1586 (C=N), 1720 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.23 (s, 6H, 2×$COCH_3$), 4.20 (bs, 1H, NH, exchangeable with D_2O), 7.26–8.70 (m, 5H, H_{arom}). **Entry 40**. IR cm^{-1} (KBr): 3300, 3460 (NH_2), 1720 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.35 (s, 6H, $COCH_3$), 7.06–7.95 (m, 6H, H_{arom}). **Entry 41**. IR cm^{-1} (KBr): 3300, 3460 (NH_2), 1700 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.23 (s, 3H, $COCH_3$), 2.34 (s, 3H, $ArCH_3$),

Table 2. Microwave-assisted N-, O- and S-acetylations using Ac_2O–Py/basic alumina (power = 300 W)

Entry	Reactant	Product	Temperature (°C)	Time (min)	Yield (%)	mp/Lit. mp (°C)
1.	Hydrazine	Hydrazine acetate	102–04	1	100	100/100–102[25]
2.	Hydrazine	Hydrazine diacetate	131–33	5	100	129–30
3.	Butylamine	*N*-Butylacetamide	113–15	1.5	75	228/229 (bp)[26]
4.	Cyclohexylamine	*N*-Cyclohexylacetamide	108–10	1	75	102–03/104[27]
5.	Aniline	Acetanilide	93–95	1	100	11–14/113–15[27]
6.	*o*-Anisidine	2-Methoxyacetanilide	123–25	2	92	86–87/88[27]
7.	*m*-Toluidine	3-Methylacetanilide	129–31	2	96	64–65/66[27]
8.	*p*-Anisidine	4-Methoxyacetanilide	130–32	2	80	129–30/130[27]
9.	*p*-Toluidine	4-Methylacetanilide	125–27	2	98	152–53/154[27]
10.	2-Nitroaniline	2-Nitroacetanilide	119–21	16	74	93–94/94[27]
11.	3-Nitroaniline	3-Nitroacetanilide	98–100	2	88	154–54/155[27]
12.	4-Nitroaniline	4-Nitroacetanilide	89–91	2	96	214–15/216[27]
13.	Phenol	Phenylacetate	103–05	2	100	195/196 (bp)[25]
14.	4-Methylphenol	4-Methylphenylacetate	97–99	2	81	209/210–11 (bp)[26]
15.	4-Hydroxybenzaldehyde	4-Acetoxybenzaldehyde	100–02	4	100	151–52/152–53[26]
16.	4-Hydroxybenzoic acid	4-Acetoxybenzoic acid	95–99	2	91	185–86/187[26]
17.	Vanillin	4-Acetoxy-3-methoxy-benzaldehyde	105–08	4	75	101–02/102–03[26]
18.	Quinol	1,4-Diacetoxybenzene	115–17	6	95	120–21/121[27]
19.	Resacetophenone	4-Acetoxy-2-hydroxyaceto-phenone	95–97	1	65	72–73/74[26]
20.	Resacetophenone	2,4-Diacetoxyacetophenone	120–22	1	54	36–37/38[26]
21.	Resorcinol	1,3-Diacetoxybenzene	93–96	2	92	145/146 (bp)[26]
22.	2-Nitro phenol	2-Nitro phenylacetate	106–08	6	86	39–40/41[27]
23.	4-Nitro phenol	4-Nitro phenylacetate	85–87	6	85	79–80/83[27]
24.	1-Naphthol	1-Acetoxynaphthalene	116–18	4	65	42–44/43–46[26]
25.	2-Naphthol	2-Acetoxynaphthalene	119–21	4	62	68–69/69–70[26]
26.	Morpholine	*N*-Acetylmorpholine	103–05	2	98	13–14/14[25]
27.	Piperadine	*N*-Acetylpiperadine	95–97	2	100	226/226–27 (bp)[26]
28.	Piperazine	*N*-Acetylpiperazine	77–80	0.5	75	31–32/32–34[26]
29.	Piperazine	*N*,*N*-Diacetylpiperazine	90–92	2	70	142–43/144[26]
30.	Ethylene diamine	*N*-Acetylethylenediamine	68–69	0.25	95	127/128 (bp)[26]
31.	Ethylene diamine	*N*,*N*-Diacetylethylenediamine	97–99	1	65	118–19/118–20[26]
32.	Phenyl hydrazine	Phenylhydrazineacetate	90–92	1	65	128–29/130[26]
33.	2-Amino-4-phenylthiazole	2-(*N*-acetylamino)-4-phenylthiazole	110–12	8	70	208–09
34.	2-Amino-4-(4-methylphenyl)-thiazole	2-(*N*-acetylamino)-4-(4-methyl-phenyl)thiazole	97–100	2	100	190–91
35.	2-Amino-4-(4-chlorophenyl)-thiazole	2-(*N*-acetylamino)-4-(4-chloro-phenyl)thiazole	98–100	13	90	230–31
36.	2-Amino-4-(4-bromophenyl)-thiazole	2-(*N*-acetylamino)-4-(4-bromo-phenyl)thiazole	95–99	13	72	233–34
37.	2-Amino-4-(4-fluorophenyl)-thiazole	2-(*N*-acetylamino)-4-(4-fluoro-phenyl)thiazole	102–05	4	70	224–25
38.	2-Amino-4-(4-hydroxyphenyl)-thiazole	2-Amino-4-(4-acetoxyphenyl)-thiazole	62–65	0.5	100	218–19
39.	2-Amino-4-(4-hydroxyphenyl)-thiazole	2-(*N*-acetylamino)-4-(4-acetoxy-phenyl)thiazole	96–99	16	100	225–26
40.	2-Aminobenzenethiol	1-Thioacetoxy-2-*N*-acetylamino-benzene	122–25	10	74	133–34/135[28]
41.	2-Amino-5-methylbenzene-thiol	2-Amino-5-methylthio-acetoxy-benzene	68–70	1	96.4	204–05
42.	2-Amino-5-ethoxybenzene-thiol	2-Amino-5-ethoxythio-acetoxy-benzene	70–72	0.5	95	178–79
43.	2-Amino-5-chlorobenzene-thiol	2-Amino-5-chlorothio-acetoxy-benzene	85–89	2	71.5	238–39
44.	2-Amino-5-bromobenzene-thiol	2-Amino-5-bromothio-acetoxy-benzene	82–85	2	82.5	243–44

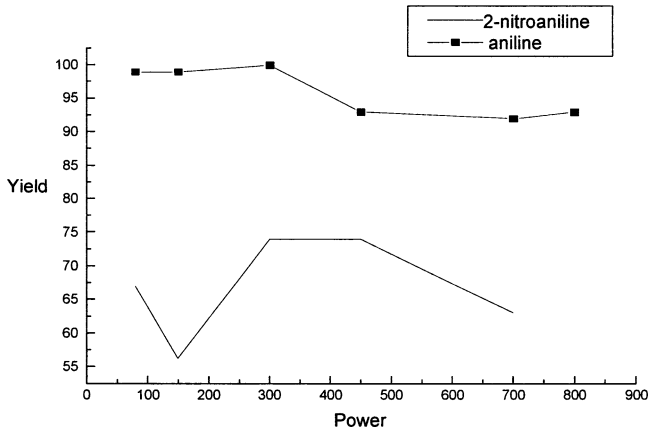


Figure 1. Effect of MW power on the yield of acetylation of aniline and 2-nitroaniline.

Table 3. Comparison of results using the microwave method (MW) and oil-bath (Δ) for acetylations of different isomeric nitroanilines (power = 300 W)

Entry	Method	Time (min)	Temperature[a] (°C)	Yield[b] (%)
10	MW	16	119–121	74
	Δ	40	120	62
11	MW	2	98–100	88
	Δ	15	100	82
12	MW	2	89–91	96
	Δ	90	90	86

[a] The final temperature is measured by immersing a glass thermometer into the reaction mixture at the end of exposure during the microwave experiment.
[b] Yield of isolated products.

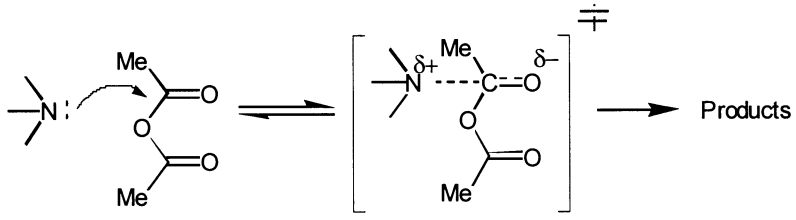
6.95–7.33 (m, 3H, H_{arom}), 8.15 (bs, 2H, NH_2, exchangeable with D_2O). **Entry 42**. IR cm^{-1} (KBr): 3350, 3450 (NH_2), 1750 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 1.53 (t, 3H, OCH_2CH_3), 2.13 (s, 3H, $COCH_3$), 3.93 (q, 2H, OCH_2CH_3), 7.06–7.33 (m, 3H, H_{arom}), 8.06 (bs, 2H, NH_2, exchangeable with D_2O). **Entry 43**. IR cm^{-1} (KBr): 3250, 3400 (NH_2), 1700 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H, $COCH_3$), 7.4–7.8 (m, 3H, H_{arom}), 8.17 (bs, 2H, NH_2, exchangeable with D_2O). **Entry 44**. IR cm^{-1} (KBr): 3255, 3400 (NH_2), 1700 ($COCH_3$); ^1H NMR ($CDCl_3$): δ 2.3 (s, 3H, $COCH_3$), 7.36–7.70 (m, 3H, H_{arom}), 8.05 (bs, 2H, NH_2, exchangeable with D_2O).

Acknowledgements

We thank Dr. G. N. Qazi, director, R.R.L. Jammu for extending library and instrumentation facilities.

References

1. Pearson, A. L.; Roush, W. J. *Handbook of Reagents for Organic Synthesis*: *Activating Agents and Protecting Groups*; John Wiley and Sons: UK, 1999; pp. 9–16.
2. Höfle, G.; Steglich, V.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583.
3. Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358–3359.
4. Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702–5703.
5. D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963–2966.
6. Yadav, V. K.; Babu, K. G.; Mittal, M. *Tetrahedron* **2001**, *57*, 7047–7051.
7. Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, *57*, 2001–2007.
8. (a) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413–4414; (b) Zhao, H.; Pendri, A.; Greenwald, R. B. *J. Org. Chem.* **1998**, *63*, 7559–7562.
9. Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265–266.
10. Miyashita, M.; Shiina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516–1527.
11. Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141–142.
12. Mukaiyama, T.; Shiina, I.; Miyashita, M. *Chem. Lett.* **1992**, 625–628.
13. Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1999**, *40*, 2611–2614.
14. (a) Li, A.-X.; Li, T.-S.; Ding, T.-H. *Chem. Commun.* **1997**, 1389–1390; (b) Bhaskar, P. M.; Loganathan, D. *Tetrahedron Lett.* **1998**, *39*, 2215–2218.
15. Allevi, P.; Ciuffreda, P.; Longo, A.; Anastasia, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2915–2924.
16. Yamada, S.; Sugaki, T.; Matsuzaki, K. *J. Org. Chem.* **1996**, *61*, 5932–5938.
17. Ballini, R.; Bosica, G.; Carloni, S.; Ciaralli, L.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1998**, *39*, 6049–6052.
18. Gedye, R. J.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279–282.
19. Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4948.



Scheme 1.

20. (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (b) De la Hoz, A.; Diaz-Ortiz, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659–3673; (c) Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, *29*, 239–249; (d) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851–10870; (e) Varma, R. S. *Green Chem.* **1999**, *1*, 43–55; (f) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213–1234; (g) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432; (h) Abramovitch, R. A. *Org. Prep. Proc. Int.* **1991**, *2*, 685–711.
21. (a) Kwon, P. S.; Kim, J. K.; Kwon, T. W.; Kim, Y. H.; Chung, S. K. *Bull. Korean Chem. Soc.* **1997**, *18*, 1118–1119; (b) Karmakar, D.; Prajapati, D.; Sandhu, J. S. *J. Chem. Res. (S)* **1998**, 382–383; (c) Kalita, D. J.; Borah, R.; Sarma, J. C. *J. Chem. Res. (S)* **1999**, 404–405; (d) Dekka, N.; Maroitte, A. M.; Boumendjel, A. *Green Chem.* **2001**, *3*, 263–264.
22. (a) Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2001**, *42*, 3827–3829; (b) Paul, S.; Gupta, M.; Gupta, R. *Synth. Commun.* **2001**, *31*, 67–73; (c) Paul, S.; Gupta, R.; Loupy, A.; Rani, B.; Dandia, A. *Synth. Commun.* **2001**, *31*, 711–717; (d) Paul, S.; Gupta, M.; Gupta, R. *Synlett* **2000**, 1115–1118; (e) Gupta, M.; Paul, S.; Gupta, R.; Loupy, A. *Org. Prep. Proc. Int.* **2000**, *32*, 280–283.
23. All experiments were carried out by using a 800T domestic microwave oven manufactured by BPL India Ltd, Bangalore.
24. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223.
25. Aldrich Catalog Handbook of Fine Chemicals, 2000–2001.
26. Steven, R. *Dictionary of Organic Compounds*, 4th ed.; Eyre & Spottiswoode Ltd, E. & F.N. Spon Ltd, 1971.
27. Vishnoi, N. K *Advanced Practical Organic Chemistry*, 2nd ed.; Vishal Publishing House: New Delhi, 1996.
28. Sabitha, G.; Subha Reddy, B. V.; Srividya, R.; Yadav, J. S. *Synth. Commun.* **1999**, *29*, 2311–2315.