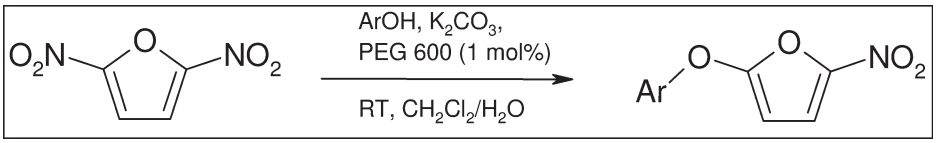
S_NAr Reaction of 2,5-Dinitrofuran: A Mild and Efficient Method for the Preparation of 2-Aryloxy-5-nitrofuran

Sandip Gavade, Kamlesh Padiya, Swapnil Bajare, Ravi Balaskar, and Dhananjay Mane*

Organic Research Laboratory, S.C.S. College, Omerga-413 606, Maharashtra, India
*E-mail: dr_dvmane@rediffmail.com

Received November 23, 2009
DOI 10.1002/jhet.537
Published online 10 December 2010 in Wiley Online Library (wileyonlinelibrary.com).



2,5-Dinitrofuran which can be easily prepared by nitration of 2-nitrofuran, on phase transfer catalysed S_NAr reaction with phenol gave good yield of 2-aryloxy-5-nitrofuran.

J. Heterocyclic Chem., **48**, 458 (2011).

INTRODUCTION

Oxygen-containing heterocycle namely furans are important constituents of a variety of important classes of pharmacologically active compounds. These compounds are known to exhibit different activities, such as lipogenes inhibitors [1], antiarrhythmics [2], potassium channel blockers [3], antimicrobials such as antimalarials [4], EGFR (HER-1, erbB 1) inhibitors [5], cyclogenes-2 inhibitors [6], protein tyrosin kinase inhibitors [7], anaesthetics [8], 5-HT1D receptor antagonists [9], and nonsteroidal antiinflammatory drugs [10].

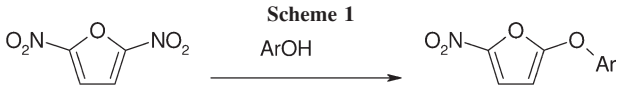
Initial attempt to react phenol with 2-chloro-5-nitrofuran under different neutral, basic, and phase transfer catalyst condition were unsuccessful. Starting material could not be isolated, which indicates 2-chloro-5-nitrofuran is unstable. In this communication, we report the mild and efficient phase transfer catalyzed S_NAr reaction of 2,5-dinitrofuran with phenols. The nucleophilic substitution of nitro group in furan derivatives like 5-nitro-2-furancarbaldehyde, with different nucleophiles like phenoxide [11], alkoxide [12], hydrogen halide [13], azide, arylmercaptides, benzenesulfinate [14], have been reported. The similar reactions with other furan derivatives like 5-nitro-2-furancarboxylate [15–17], 5-nitro furfurylnitrate [18], and 5-nitro-2-furfurylidenemalononitrile [19], since the 2-nitrofuran derivative is available easily than corresponding 2-halofuran analogs, the former becomes the synthetic equivalent of choice 2-furyl synthon. To overcome this problem we have used 2,5-dinitrofuran as comparatively more stable alternative to 2-chloro-5-nitrofuran. Only a few examples have been reported literature for nucleoplilic substitution of 2,5-dinitrofuran [20–22], The nulceophiles used in majority of these reports are soft carbon nucleophiles like anions derived from ethyl acetate or diethyl malonate, benzenesulphonates, thiophenolates, and amines [23]. However, there is no report of reaction of 2,5-dinitrofuran with phenol.

RESULTS AND DISCUSSION

2,5-Dinitrofuran can be readily prepared from 2-nitrofuran by treatment of conc. HNO_3 [23]. 2,5-Dinitrofuran can under go S_NAr substitution reaction to yield 2-substituted-5-nitrofuran. The S_NAr substitution in case of 5-nitro-2-furancarbaldehyde [11] and 5-nitro-2-furancarboxylate [16,17] is reported to give good yield with NaH in DMSO. The same method when used for the preparation of 2-substituted-5-nitrofuran from 2,5-dinitrofuran, it gave a very poor yield of desired product. We have carried out a series of reactions with different base and solvent combinations to optimize the reaction conditions (Scheme 1). The results are shown in Table 1. It was found that high temperature or strong base resulted in poor yield of desired product. Instability of dinitrofuran could possibly be the reason for poor yield as the unreacted nitro compound could not be isolated from the reaction mixture. This reaction thus demands a mild condition. It was observed that reaction goes smoothly in biphasic system (entry 9; Table1), and the rate of reaction accelerates by addition of Phase transfer Catalyst 18Crown6 (entry 10; Table 1).

Effect of type of catalyst on condensation of 3-hydroxyquinoline and 2,5-dinitrofuran was then studied using different phase transfer catalysts and conditions. The results are shown in Table 2. It reveals that poly ethylene glycol 600 (PEG 600), which is the most economic, is also equally efficient to catalyze the reaction. Kinetics of this reaction was studied by ^1H NMR of the reaction aliquots with 0, 0.1, 1, 2, and 5 mol % of PEG

Scheme 1



600. The results are shown in Figure 1. It appears from the study that 1 mol % is the minimum requirement of catalyst that gives 90% conversion in about 3 h.

The optimized condition of 1.0 mol % of PEG 600 was used for the reactions with different phenols. (Scheme 2); the results are displayed in Table 3. Electron withdrawing substituents such as F, NO_2, and Ph groups facilitates the reaction allowing shorter reaction times and yield was high (entry 3,4,5, and 11, Table 3). Electron donating substituents OMe and Me groups require comparatively longer time and low yield (entry 2,6, and 12, Table 3).

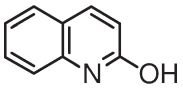
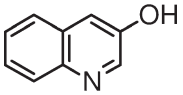
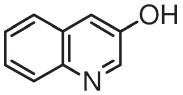
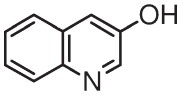
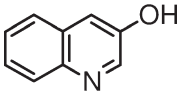
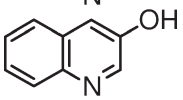
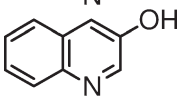
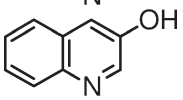
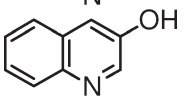
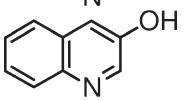
In Conclusion, A mild and efficient method for the preparation of 2-aryloxy-5-nitrofuran is developed. It provides the first example of phase transfer catalyzed S_NAr reaction of 2,5-dinitrofuran.

EXPERIMENTAL

2-Nitrofuran and 18crown6 were purchased from Aldrich. Commercial solvents and reagents were used as received. Flash column chromatography was performed over silica gel H (100–200 or 200–300 mesh) using hexane/ethyl acetate. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on either 300 MHz spectrometer. NMR chemical shifts were reported in δ (ppm) using the δ 2.54 signal of DMSO (^1H NMR) and the δ 39.94 signal of DMSO (^{13}C NMR) as internal standards. Mass spectra were recorded using either chemical

Table 1

Screening of reaction condition for the substitution of nitro from 2,5-dinitrofuran by Ar—OH.

Sr. No.	Ar—OH	Base	Solvent	Temp. °C	Catalyst	Yield[a] (%)
1		Cs_2CO_3	DMF	RT	–	5
2		Cs_2CO_3	DMF	60	–	6
3		K_2CO_3	DMF	RT	–	3
4		TEA	CH_3CN	RT	DMAP[b]	0
5		–	DMF	RT	KF[c]	0
6		–	DMF	60	–	0
7		–	CH_2Cl_2	RT	–	0
8		–	CH_2Cl_2/H_2O	RT	–	0
9		K_2CO_3	CH_2Cl_2/H_2O	RT	–	33
10		K_2CO_3	CH_2Cl_2/H_2O	RT	18Crown6[b]	89

[a] The yields reported are after isolation and purification by the column chromatography.
[b] 0.1 mol %.
[c] 1.0 mmol.

Table 2

Optimization of type and quantity of phase transfer catalyst for S_NAr reaction of 2,5-dinitrofuran with phenol in CH_2Cl_2:Water (1:1) at room temperature.

Sr. No.	PTC	Mol % of PTC	Yield[a] (%)
1	18 Crown 6	1	90
2	PEG 600	5	98
3	PEG 600	2	99
4	PEG 600	1	98
5	PEG 600	0.1	89
6	PEG 600	0.01	83

[a] The yields reported are after isolation and purification by the column chromatography.

ionization or electron impact ionization. Thin layer chromatography was used to monitor reaction progress.

Typical procedure for the synthesis of 2,5-dinitrofuran. A mixture of 5.8 g (50 mmol) of 2-nitrofuran and 100 mL of conc. HNO_3(70%) was heated to 60°C for 4 h. Mixture was then cool to room temperature diluted with 100 mL of cold water and neutralized with Na_2CO_3 solution. Extracted with CH_2Cl_2. Combined organic layer washed with brine and dried over anhydrous Na_2SO_4. Recrystallisation from ethanol gave 4.0 g of 2,5-dinitrofuran as a yellow solid, mp 100°C.

Typical procedure for the synthesis of compounds 1–14 using PEG 600. Mixture of 2,5-dinitrofuran (1.0 mmol), phenol (1.0 mmol), and K_2CO_3 (1.0 mmol) was taken in 3.0 mL mix of 1:1 dichloromethane (CH_2Cl_2) and water. PEG 600 (0.01 mmol) was then added and mixture was stirred at room temperature till the good conversion was observed on TLC. Organic layer separated. Aqueous layer washed with CH_2Cl_2. Combined organic layer washed with water and then with brine. Organic layer dried over anhydrous Na_2SO_4, evaporated and purified by column chromatography.

3-[(5-Nitro-2-furyl)oxy]quinoline: (Table 1, entry 10). Yellow solid, yield 89%; mp 167–170°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.30(1H, d, J = 3.8 Hz, F H-4), 7.69(1H, m,), 7.81(1H, td, J = 7.7, 1.5 Hz,), 7.85(1H, d, J = 4.2 Hz, F H-3), 8.02(1H, d, J = 6.8 Hz,), 8.10(1H, d, J = 8.7 Hz,), 8.41(1H, d, J = 2.6 Hz,), 9.01(1H, d, J = 2.6 Hz,); ^{13}C NMR (DMSO, 75 MHz) : δ = 157.8, 147.8, 145.9, 144, 129.9, 129.3, 128.5, 128.3, 123.2, 117.7, 93.6. HRMS (EI, *m*/*e*) calcd for $C_{13}H_8N_2O_4$ (M^+) 256.22, found 256.02.

2-Nitro-5-phenoxyfuran: (Table 2, entry 1). Brown solid, yield 79%; mp 53–55°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.04(1H, d, J = 3.8 Hz, F H-4), 7.35(3H, m, P H), 7.50(2H, m, P H), 7.79(1H, d, J = 3.8 Hz, F H-3). HRMS (EI, *m*/*e*) calcd for $C_{10}H_7NO_4$ (M^+) 205.17, found 204.96.

2-(4-Methoxyphenoxy)-5-nitrofuran: (Table 2, entry 2). Brown solid, yield 82%; mp 69–71°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 3.77(3H, s, CH_3), 5.86(1H, d, J = 3.8 Hz, F H-4), 7.05(2H, m, P H), 7.30(2H, m, P H), 7.76(1H, d, J = 3.8 Hz, F H-3); ^{13}C NMR (DMSO, 75 MHz) : δ = 159.8, 177.7, 147.1, 120.8, 118,115.7, 91.3. HRMS (EI, m/e) calcd for $C_{11}H_9NO_5$ (M^+) 235.19, found 235.02.

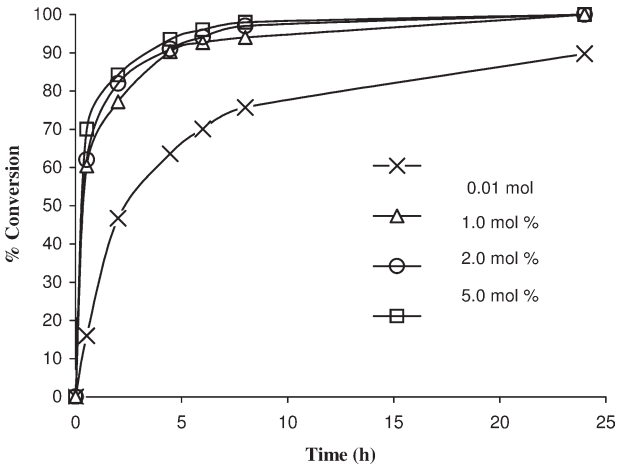


Figure 1. Effect of PTC concentration on kinetics of S_NAr reaction of 2,5-dinitrofuran with phenol in CH_2Cl_2: water (1:1) at room temperature.

2-(4-Fluorophenoxy)-5-nitrofuran: (Table 2, entry 3). Yellow solid, yield 96%; mp 73–75°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.00(1H, d, J = 3.8 Hz, F H-4), 7.35(2H, m, P H), 7.44(2H, m, P H), 7.78(1H, d, J = 3.8 Hz, F H-3); ^{13}C NMR (DMSO, 75 MHz): δ = 161.3, 158.4, 158.1, 149.6, 149.5, 144.0, 121.1, 120.9, 117.5, 117.2, 116.9, 91.8. HRMS (EI, *m*/*e*) calcd for $C_{10}H_6FNO_4$ (M^+) 223.16, found 223.02.

2-Nitro-5-(4-nitrophenoxy)furan: (Table 2, entry 4). Yellow solid, yield 98%; mp 87–90°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.40(1H, d, J = 4.2 Hz, F H-4), 7.59(2H, m, P H), 7.85(1H, d, J = 4.2 Hz, F H-3), 8.35(2H, m, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 163.9, 158.6, 155.3, 144.8, 144.7, 126.3, 126.1, 118.8, 116.7, 115.7, 95.2. HRMS (EI, *m*/*e*) calcd for $C_{10}H_6N_2O_6$ (M^+) 250.16, found 249.95.

2-(Biphenyl-4-yloxy)-5-nitrofuran: (Table 2, entry 5). Yellow solid, yield 97%; mp 153–156°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.13(1H, d, J = 4.2 Hz, F H-4), 7.45(5H, m, P H), 7.71(2H, m, P H), 7.78(3H, m, P H); ^{13}C NMR (DMSO, 75 MHz) : δ = 158.3, 153.6, 139.3, 138.6, 129.4, 129.1, 128.1, 127.1, 119.5, 117.9, 93.1. HRMS (EI, *m*/*e*) calcd for $C_{16}H_{11}NO_4$ (M^+) 281.27, found 281.05.

2-Methyl-5-[(5-nitrofuran-2-yl)oxy]pyridine: (Table 2, entry 6). Yellow solid, yield 83%; mp 122–124°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.50(3H, s, CH_3), 6.09(1H, d, J = 4.2 Hz, F H-4), 7.40(1H, d, J = 8.7 Hz, P H), 7.76(1H, dd, J = 8.7, 3.0 Hz, P H), 7.79(1H, d, J = 4.2 Hz, F H-3), 8.53(1H, d, J = 3.0 Hz, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 157.9, 156.1, 148.5, 144.1, 139.9, 127.1, 124.3, 117.4, 92.0. HRMS (EI, *m*/*e*) calcd for $C_{10}H_8N_2O_4$ (M^+) 220.18, found 220.02.

Scheme 2

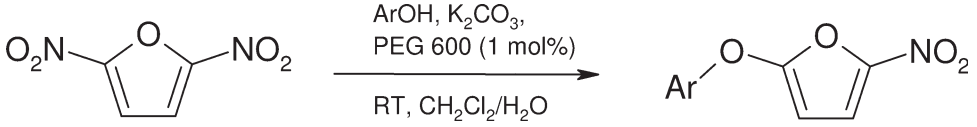
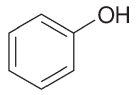
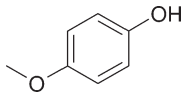
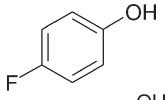
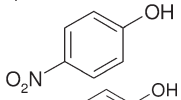
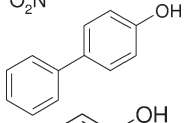
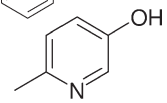
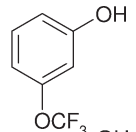
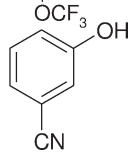
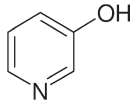
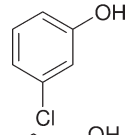
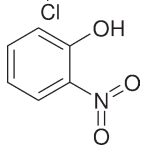
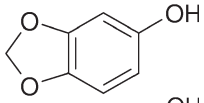
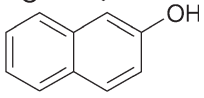
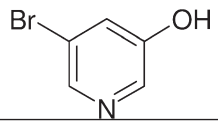


Table 3

PTC catalyzed S_NAr reaction of 2,5-dinitrofuran with different phenols (Scheme 2).

S. No.	Ar	Time (h)	Isolated yield[a] (%)
1		4	79
2		4	82
3		3	96
4		2	98
5		2	97
6		3	83
7		4	77
8		4	85
9		3	98
10		1	79
11		2	97
12		1	84
13		1	87
14		4	85

[a] The yields reported are after isolation and purification by the column chromatography.

2-Nitro-5-[3-(trifluoromethoxy)phenoxy]furan: (Table 2, entry 7). Yellow liquid, yield 77%. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.21(1H, d, J = 5.3 Hz, F H-4), 7.40(2H, m, P H), 7.49(1H, s, P H), 7.64(1H, m, P H), 7.81(1H, d, J = 5.3 Hz, P H); HRMS (EI, *m*/*e*) calcd for $C_{11}H_6F_3NO_5$ (M^+) 289.16, found 289.01.

3-[(5-Nitrofuran-2-yl)oxy]benzonitrile: (Table 2, entry 8). White solid, yield 85%; mp 112–116°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.25(1H, d, J = 4.2 Hz, F H-4), 7.70(2H, m, P H), 7.81(2H, m, P H), 7.95(1H, m, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 156.5, 153.9, 131.8, 130.0, 123.7, 122.0, 117.6, 117.0, 113.1, 93.8. HRMS (EI, *m*/*e*) calcd for $C_{11}H_6N_2O_4$ (M^+) 230.18, found 230.02.

3-[(5-Nitrofuran-2-yl)oxy]pyridine: (Table 2, entry 9). White solid, yield 98%; mp 88–91°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.18(1H, d, J = 3.8 Hz, F H-4), 7.56(1H, dd, J = 7.7, 4.7 Hz, P H), 7.81(1H, d, J = 3.8 Hz, F H-3), 7.87(1H, ddd, J = 8.5, 2.8, 1.1 Hz, P H), 8.56(1H, dd, J = 4.5, 1.1 Hz, P H), 8.68(1H, d, J = 3.0 Hz, P H); HRMS (EI, *m*/*e*) calcd for $C_9H_6N_2O_4$ (M^+) 206.16, found 206.09.

2-(3-Chlorophenoxy)-5-nitrofuran: (Table 2, entry 10). Yellow liquid, yield 79%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.18(1H, d, J = 4.2 Hz, F H-4), 7.34(1H, m, P H), 7.41(1H, m, P H), 7.53(2H, m, P H), 7.80(1H, d, P H); HRMS (EI, *m*/*e*) calcd for $C_{10}H_6ClNO_4$ (M^+) 239.61, found 239.02.

2-Nitro-5-(2-nitrophenoxy)furan: (Table 2, entry 11). Yellow solid, yield 97%; mp 97–99°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.20(1H, d, J = 4.2 Hz, F H-4), 7.59(2H, m, P H), 7.85(1H, d, J = 4.2 Hz, F H-3), 8.35(2H, m, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 157.0, 145.8, 144.8, 140.7, 136.4, 127.9, 126.7, 122.4, 117.6, 93.3. HRMS (EI, *m*/*e*) calcd for $C_{10}H_6N_2O_6$ (M^+) 250.16, found 249.95.

5-[(5-Nitrofuran-2-yl)oxy]-1,3-benzodioxole: (Table 2, entry 12). Yellow solid, yield 84%; mp 96–98°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 5.92(1H, d, J = 4.2 Hz, F H-4), 6.10(2H, s, CH_2), 6.83(1H, m, P H), 6.99(1H, d, J = 8.7 Hz, P H), 7.09(1H, d, J = 2.6 Hz, P H), 7.76(1H, d, J = 3.8 Hz, F H-3); ^{13}C NMR (DMSO, 75 MHz): δ = 159.5, 148.2, 147.6, 145.5, 143.8, 117.7, 11.9, 108.5, 102.1, 101.6, 91.2. HRMS (EI, *m*/*e*) calcd for $C_{11}H_7NO_6$ (M^+) 249.18, found 249.15.

2-(Naphthalen-2-yloxy)-5-nitrofuran: (Table 2, entry 13). Brown solid, yield 87%; mp 73–76°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.15(1H, d, J = 4.2 Hz, F H-4), 7.55(3H, m, P H), 7.82(1H, d, J = 3.8 Hz, F H-3), 7.87(1H, d, J = 2.6 Hz, P H), 7.97(2H, dt, J = 9.3, 7.3 Hz, P H), 8.08(1H, d, J = 9.1 Hz, P H); ^{13}C NMR (DMSO, 75 MHz): δ = 158.5, 151.5, 144.7, 133.9, 131.4, 131.1, 128.2, 128.0, 127.6, 126.5, 118.8, 117.9, 115.5, 93.2 ppm. HRMS (EI, *m*/*e*) calcd for $C_{14}H_9NO_4$ (M^+) 255.23, found 255.08.

3-Bromo-5-[(5-nitrofuran-2-yl)oxy]pyridine: (Table 2, entry 14). White solid, yield 85%; mp 106–109°C. ^{1}H NMR (DMSO-d_6, 300MHz) δ: 6.30(1H, d, J = 4.2 Hz, F H-4), 7.81(1H, d, P H), 8.28(1H, m, P H), 8.70(2H, t, J = 1.9 Hz, P H); ^{13}C NMR (DMSO, 75 MHz) : δ = 156.4, 150.7, 147.9, 144.5, 139.4, 129.2, 120.2, 117.0, 93.7. HRMS (EI, *m*/*e*) calcd for $C_9H_5BrN_2O_4$ (M^+) 285.05, found 284.01.

REFERENCES AND NOTES

[1] Summers, J. B.; Gunn, B. P.; Broos, D. W.; Holms, J. H. PCT Int Appl, WO 8904299 A1 890518, 1989, pp 71.

[2] Pelosi, S. S., Jr.; Yu, C. N. PCT Int Appl, WO 9304060 A1 930304, 1993, pp 57.

[3] Pelosi, S. S., Jr.; Yu, C. N.; Calcagno, M. A. US Patent 5,462,940, 1995.

[4] Hall, J. E.; Tidwell, R. R.; Boykin, D. W. US Patent 5,843,980, 1998.

[5] Clive, C. M.; Stuart, C. G.; Barry, G. S.; Elizabeth, L. K.; Jane, S. K. US Patent 6,727,256, 2004.

[6] Burdan, F.; Dudka, J.; Szumilo, J.; Korobowicz, A.; Klepacz, L. Reprod Toxicol 2003, 17, 413.

[7] (a) Carter, M. C.; Cockerill, G. S.; Guntrip, S. B.; Lackey, K. E.; Smith, K. J. US Patent 6,727,256, 1999; (b) Cockerill, G. S.; Lackey, K. E. US Patent 66,933,299. 2000.

[8] Krause, T.; Gerbershagen, M. U.; Fiege, M.; Wisshorn, R.; Wappler, F. Anaesthesia 2004, 59, 364.

[9] Scopes, D. I. C.; Clitherow, J. W.; Mitchell, W. L.; Carter, M. UK Pat Appl, GB 2276164 A1 940921, 1994, pp 44.

[10] Peterson, J. W.; Gessell-Lee, D. L.; Saini, S. S. EP 1353664, 2003.

[11] Horisawa, E.; Danjo, K.; Haruna, M. Drug Dev Ind Pharm 2000, 26, 1271.

[12] Murakami, N.; Aihara, S.; Iwata, K.; Saito, T.; Naruse, T. Jpn J Pharmacol 1999, 79, 439.

[13] Tanaka, A.; Usiu, T.; Shimadzu, M. Chem Pharm Bull 1980, 28, 2846.

[14] Olivered, J.; Heotis, J. P. J Org Chem 1968, 33, 2552.

[15] Snyder, H. R., Jr.; Seehausen, P. H. J Heterocycl Chem 1973, 10, 385.

[16] Lieb, F.; Eiter, K. Ann Chem 1972, 761, 130.

[17] Tanaka, A.; Usiu, T.; Shimadzu, M. J Heterocycl Chem 1981, 18, 1241.

[18] Kuo, C. H.; Wu, J. S.; Huang, L. J.; Wu, C. H.; Chou, T. C. J Heterocycl Chem 1989, 26, 605.

[19] Yamamoto, K.; Koyanagi, J.; Horie, I.; Ogawa, M.; Sakuma, K.; Tanaka, A. Chem Pharm Bull 1995, 43, 2064.

[20] Povazanec, F.; Kovak, J.; Hesek, D. Collect Czech Chem Commun 1979, 44, 3301.

[21] Knoppova, V.; Kada, R.; Kovak, J. Collect Czech Chem Commun 1979, 44, 2417.

[22] Shimadzu, M.; Ishikawa, N.; Yamamoto, K.; Tanaka, A. J Heterocyclic Chem 1986, 23, 1179.

[23] Stegel, F.; Doddi, G.; Porreti, A. J Heterocycl Chem 1974, 11, 97.