DOI: 10.1002/ejoc.200801115

Preparation of Triaryl- and Triheteroarylmethanes under Ytterbium Triflate Catalysis and Solvent-Free Conditions

Salvatore Genovese,*[a] Francesco Epifano,[a] Caroline Pelucchini,[b] and Massimo Curini[b]

Keywords: Triarylmethanes / Triheteroarylmethanes / Ytterbium / Activated arenes / Condensation reactions

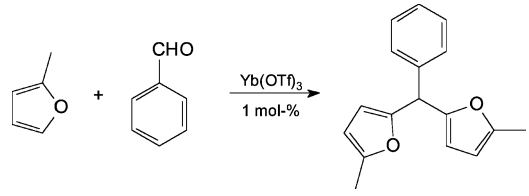
Triaryl- and triheteroarylmethanes have been synthesized in very good yield under solvent-free conditions from differently substituted aldehydes and 2-methylfuran or methoxybenzene in the presence of $Yb(OTf)_3$ as catalyst.

Introduction

During the last 15 years, rare earth metal triflates have been found to be unique Lewis acids in that they are water-tolerant reusable catalysts and can effectively promote several carbon–carbon and carbon–heteroatom bond-formation reactions in high yield.[1,2] In continuation of our ongoing studies aimed at developing mild and practical protocols for the synthesis of useful building blocks and/or biologically active compounds by using $Yb(OTf)_3$ as a catalyst and employing water as solvent or solvent-free conditions, it was speculated that this lanthanide salt, which has recently been shown to catalyse a variety of valuable and good yielding C–C bond-forming reactions;[3] might be ideal for effecting the condensation of aldehydes with activated arenes in the synthesis of triaryl- and triheteroarylmethanes. These compounds have been used as protective groups,[4] photochromic agents,[5] and dyes[6] and have been extensively used as key intermediates in synthetic, medicinal, and industrial chemistry.[7] Ring-hydroxylated triarylmethanes have been also reported to exhibit antitumor and antioxidant activities.[8] Moreover diheteroarylmethanes are of interest to the food industry as natural components of certain food and beverage items as well as flavour agents in coffee.[9] Despite their importance, the synthesis of triaryl- and triheteroarylmethanes has received to date little attention. Although a number of methods for the synthesis of triarylmethanes are available, most of them suffer major or minor limitations in that they are multi-step processes, require harsh reaction conditions[10] with low yields, tedious workup procedures with low selectivities and co-occurrence of several side reactions, which makes chromatography for the purification of the adducts necessary.[11,12]

Results and Discussion

Herein, we wish to report that, by the appropriate choice of the reaction conditions, ytterbium triflate can be conveniently used for the preparation of triaryl- and triheteroarylmethanes in high yield. Thus, reaction of 2-methylfuran with benzaldehyde in the presence of $Yb(OTf)_3$ under solvent-free conditions (Scheme 1) was used as model. The reaction was carried out at room temperature for 4 h by using commercially available benzaldehydes (1 mmol) and 2-methylfuran (1 mmol) in the presence of $Yb(OTf)_3$ hydrate (1 mol-% based on the aldehyde) as catalyst.



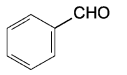
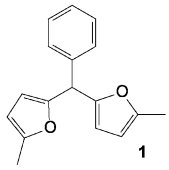
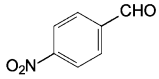
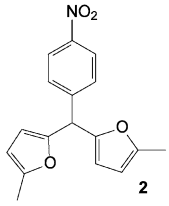
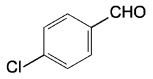
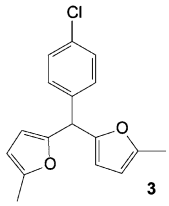
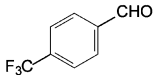
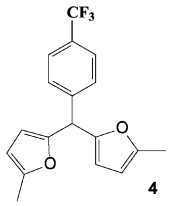
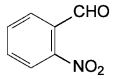
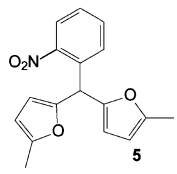
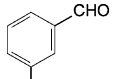
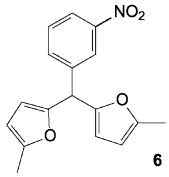
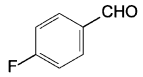
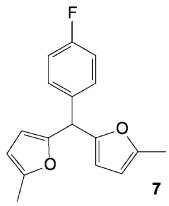
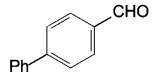
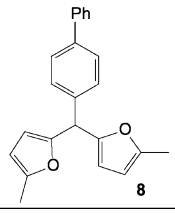
Scheme 1.

After the addition of 1 N NaOH to precipitate Yb^{III} as the corresponding hydroxide, the desired product was obtained in 98% yield after filtration and extraction with Et_2O (3×5 mL). On the basis of the above-cited result, a variety of substituted benzaldehydes were investigated for the catalytic activity of $Yb(OTf)_3$. As shown in Table 1 the desired triaryl- and triheteroarylmethanes were selectively obtained in excellent yield.

On the basis of these results, we decided to explore the use of methoxybenzene as starting material in place of 2-methylfuran, by performing the reaction under the same conditions as described above.

[a] Dipartimento di Scienze del Farmaco, Università "G. D'Annunzio di Chieti-Pescara",
Via dei Vestini 31, 66013 Chieti Scalo (CH), Italy
E-mail: sgenovese@unich.it
[b] Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università degli Studi di Perugia
Via del Liceo 1, 06123 Perugia, Italy
Fax: +39-075-58551116

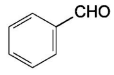
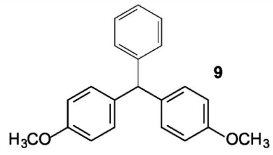
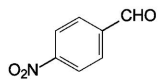
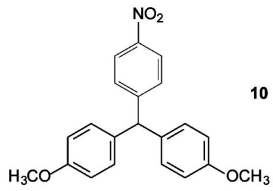
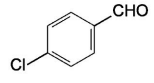
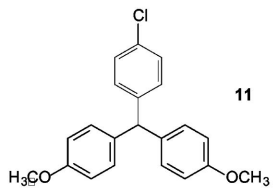
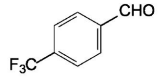
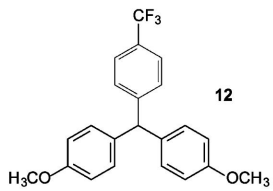
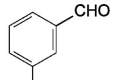
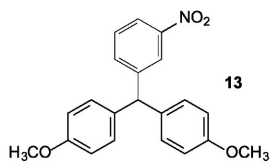
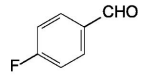
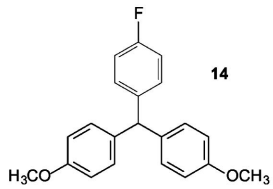
Table 1. $Yb(OTf)_3$-catalyzed formation of trietheroarylmethanes by reaction of 2-methylfuran with substituted benzaldehydes.

Aldehyde	Product	Yield[a] (%)
	 **1**	99
	 **2**	90
	 **3**	99
	 **4**	99
	 **5**	74
	 **6**	99
	 **7**	96
	 **8**	82

[a] Yields of pure isolated products, characterized by GC-MS, IR, ^1H NMR and ^{13}C NMR data. The degree of purity of each product listed in Table 1 was analyzed by GC/MS.

In this case, too, the corresponding adducts were obtained in very good yield (Table 2). It is important to note that the adducts were regioselectively obtained, having the new carbon–carbon bond in *para* position of the methoxybenzene ring as determined by ^1H NMR analysis. To this respect it may be supposed that the linkage of the unsubstituted benzene moiety occurred in *para* position of both anisole rings due to steric hindrance of the methoxy group.

Table 2. $Yb(OTf)_3$-catalyzed formation of trietheroarylmethanes by reaction of methoxybenzene with substituted benzaldehydes.

Aldehyde	Product	Yield[a] (%)
	 **9**	99
	 **10**	99
	 **11**	98
	 **12**	99
	 **13**	99
	 **14**	83

[a] Yields of pure isolated products, characterized by GC-MS, IR, ^1H NMR and ^{13}C NMR data. The degree of purity of each product listed in Table 1 was analyzed by GC/MS.

From every reaction the catalyst was recovered by precipitation as $Yb(OH)_3$, filtration and transformation into the triflate as already described.[13] Recycled in this way, the catalyst could be reused several times without any significant loss of activity.

The same reaction was also performed by using other metal triflates from the lanthanide series (e.g. lanthanum and europium), but the results were by far worse than with $Yb(OTf)_3$.

From a mechanistic point of view, it could be hypothesized that Yb^{III}, due to its high oxophilicity, coordinates the oxygen atom of the aldehyde, thereby enhancing the electrophilicity of the carbonyl group and thus facilitating the attack of the π-electron-rich arene.

Conclusions

In this manuscript we have demonstrated that electron-rich aromatic system undergo an efficient condensation reaction with several differently substituted benzaldehydes under the catalysis of $Yb(OTf)_3$ hydrate by means of an easy and environmentally sound method. The simple workup procedure, mild reaction conditions and high yields make our methodology a valid contribution to the existing processes in the field of triaryl- and trietheroarylmethane synthesis. Moreover, this protocol introduces a pratical and viable technology of solvent-free reactions. Further investigations to broaden the scope of this technology are in progress in our laboratories. It is reasonable to expect that the present work will find such use in the synthesis of the title compounds, which are very valuable building blocks in many respects.

Experimental Section

Synthesis of Trietheroarylmethanes. Typical Procedure: A mixture of benzaldehyde (1.0 mmol) and 2-methylfuran or methoxybenzene (2.0 mmol) was vigorously stirred with $[Yb(H_2O)_n](OTf)_3$ (0.01 mmol) at room temperature for 4 h. 1 N NaOH (2 mL) was added, the white precipitate filtered, and the resulting solution extracted with Et_2O (3 × 2 mL). The collected organic phases were dried with anhydrous Na_2SO_4, and the solvent was evaporated to dryness to give the desired trietheroarylmethanes in pure form. The degree of purity of each product listed in Table 1 was analyzed by GC/MS with a Hewlett Packard 6890 gas chromatograph equipped with a 12.5 mm × 0.25 mm MetSil column couplet to HP Chem Station Software. The carrier gas was helium at a pressure of 3.5 kg/cm^2, and the column temperature was programmed from 50 to 270 °C at 10 °C/min. The chromatogram was obtained by using a reporting integrator. Mass spectra were obtained from a GC-MS system operating in the EI mode at 70eV, equipped with a 12.5 mm × 0.25 mm MetSil column and an HP5973 Mass Selective Detector, by using the same chromatographic conditions reported above. The column was connected to the mass spectrometer in-source through an open-split interface heated at 250 °C. ^{1}H and ^{13}C NMR spectra were recorded by using the same general procedure as already reported in ref.[17]

2-Methyl-5-[(5-methyl-2-furyl)(phenyl)methyl]furan (1): Yellow solid; m.p. 95–100 °C. ^{1}H NMR: see ref.[12] ^{13}C NMR: see ref.[12] $C_{17}H_{16}O_2$ (252.31): calcd. C 80.93, H 6.39, O 12.68; found C80.88, H 6.35, O 12.62.

2-Methyl-5-[(5-methyl-2-furyl)(4-nitrophenyl)methyl]furan (2): Yellow solid; m.p. 89–91 °C. ^{1}H NMR: see ref.[14] ^{13}C NMR: see ref.[14] $C_{17}H_{15}NO_4$ (297.31): calcd. C 68.68, H 5.09, N 4.71, O 21.5; found C 68.60, H 5.01, N 4.67, O 21.49.

5-[(4-Chlorophenyl)(5-methyl-2-furyl)methyl]-2-methylfuran (3): Pale yellow solid; m.p. 95–100 °C. ^{1}H NNR (200 MHz, $CDCl_3$; Me_4Si): δ = 2.27 (2 s, 6 H, CH_3), 5.89 (s, 1 H, Ar_3CH), 7.18–7.37 (m, 8 H, aromatic H) ppm. ^{13}C NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 13.35, 48.39, 104.59, 105.02, 129.08, 131.65, 132.21, 135.73, 147.45, 151.33 ppm. $C_{17}H_{15}ClO_2$ (286.76): calcd. C 71.21, H 5.27, Cl 12.36, O 11.1; found C 71.17, H 5.23, Cl 12.32, O 11.11. MS: *m*/*z* (%) = 286 (100) [M$^+$], 51 (9), 75 (8), 89 (6), 102 (2), 115 (10), 128 (5), 141 (12), 162 (5), 175 (100), 189 (6), 208 (49), 229 (8), 243 (48), 271 (15).

2-Methyl-5-{(5-methyl-2-furyl)[4-(trifluoromethyl)phenyl]methyl}-furan (4): Pale yellow solid; m.p. 91–96 °C. ^{1}H NMR: see ref.[15] ^{13}C NMR: see ref.[15] $C_{18}H_{15}F_3O_2$ (320.31): calcd. C 67.50, H 4.72, F 17.79, O 9.9; found C 67.47, H 4.66, F 17.75, O 9.94.

2-Methyl-5-[(5-methyl-2-furyl)(2-nitrophenyl)methyl]furan (5): Pale yellow solid; m.p. 89–91 °C. ^{1}H NMR: see ref.[14] ^{13}C NMR: see ref.[14] $C_{17}H_{15}NO_4$ (297.31): calcd. C 68.68, H 5.09, N 4.71, O 21.5; found C 68.62, H 5.03, N 4.67, O 21.48.

2-Methyl-5-[(5-methyl-2-furyl)(3-nitrophenyl)methyl]furan (6): Yellow solid; m.p. 95–96 °C. ^{1}H NMR: see ref.[14] ^{13}C NMR: see ref.[14] $C_{17}H_{15}NO_4$ (297.31): calcd. C 68.68, H 5.09, N 4.71, O 21.5; found C 68.62, H 5.03, N 4.67, O 21.48.

5-[(4-Fluorophenyl)(5-methyl-2-furyl)methyl]-2-methylfuran (7): Pale yellow solid; m.p. 90–93 °C. ^{1}H NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 2.27 (2 s, 6 H, CH_3), 5.92 (s, 1 H, Ar_3CH), 7.01–7.94 (m, 8 H, aromatic H) ppm. ^{13}C NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 13.35, 48.39, 104.59, 105.02, 110.01–110.71 (d, *J* = 28 Hz, *o*-CH), 132.61–132.88 (d, *J* = 3.2 Hz, *p*-C), 134.74–134.91 (d, *J* = 7.2 Hz, *m*-CH), 147.45, 151.33, 160.25–160.75–166.75 (d, *J* = 6 Hz, CF) ppm. $C_{17}H_{15}FO_2$ (270.30): calcd. C 75.54, H 5.59, F 7.03, O 11.8; found C 75.50, H 5.55, F 7.00, O 11.81. MS: *m*/*z* (%) = 270 (100) [M$^+$], 51 (7), 65(4), 77 (6), 95 (7), 107 (10), 120 (6), 133 (14), 146 (17), 159 (12), 175 (12), 189 (10), 213 (15), 227 (55), 241 (1), 255 (19).

2-[(1,1′-Biphenyl-4-yl)(5-methyl-2-furyl)methyl]-5-methylfuran (8): Orange solid; m.p. 99–103 °C. ^{1}H NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 2.29 (2 s, 6 H, CH_3), 5.93 (s, 1 H, Ar_3CH), 7.28–7.63 (m, 8 H, aromatic H) ppm. ^{13}C NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 13.35, 48.39, 104.57, 105.01, 126.97, 127.45, 128.66, 129.74, 136.40, 139.64, 139.94, 147.45, 151.3 ppm. $C_{23}H_{20}O_2$ (328.41): calcd. C 84.12, H 6.14, O 9.74; found C 84.09, H 6.10, O 9.71. MS: *m*/*z* (%) = 328 (100) [M$^+$], 51 (3), 77 (6), 91 (7), 103 (2), 115 (5), 131 (3), 152 (13), 175 (55), 189 (5), 202 (17), 215 (10), 228 (9), 243 (34), 270 (11), 285 (66), 313 (10).

1-Methoxy-4-[(4-methoxyphenyl)(phenyl)methyl]benzene (9): White solid; m.p. 95–100 °C. ^{1}H NMR: see ref.[16] ^{13}C NMR: see ref.[16] $C_{21}H_{20}O_2$ (304.39): calcd. C 82.86, H 6.62, O 10.51; found C 82.83, H 6.59, O 10.48.

1-[Bis(4-methoxyphenyl)methyl]-4-nitrobenzene (10): Pale yellow solid; m.p. 90–93 °C. ^{1}H NMR: see ref.[16] ^{13}C NMR: see ref.[16] $C_{21}H_{19}NO_4$ (349.39): calcd. C 72.19, H 5.48, N 4.01, O 18.32; found C 72.16, H 5.43, N 3.97, O 18.39.

1-[Bis(4-methoxyphenyl)methyl]-4-chlorobenzene (11): Pale yellow solid; m.p. 89–91 °C. ^{1}H NMR: see ref.[16] ^{13}C NMR: see ref.[16] $C_{21}H_{19}ClO_2$ (338.83): calcd. C 74.44, H 5.65, Cl 10.46, O 9.44; found C 74.40, H 5.62, Cl 10.42, O 9.41.

1-[Bis(4-methoxyphenyl)methyl]-4-(trifluoromethyl)benzene (12): Whie solid; m.p. 97–100 °C. ^{1}H NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 3.87 (2 s, 6 H, CH_3), 5.40 (s, 1 H, Ar_3CH), 6.82–8.12 (m, 8 H,

aromatic H). ^{13}C NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 54.82, 55.76, 113.56–120.69–127.83–134.96 (q, J = 285.02 Hz, CF_3) 114.04, 124.73–124.90–125.08–125.25 (q, J = 6.8 Hz, *o*-CH) 126.67–129.39–130.08–130.79 (q, J = 28.4 Hz, *C*CF_3), 129.59, 130.25–130.32–130.39–130.46 (q, J = 2.8 Hz, *m*-CH) 138.15, 149.15, 157.99 ppm. $C_{22}H_{19}F_3O_2$ (372.39): calcd. C 70.96, H 5.14, F 15.31, O 8.59; found C 70.93, H 5.11, F 15.28, O 8.53. MS: *m*/*z* (%) = 372 (70) [M^+], 53 (6), 77 (4), 95 (3), 115 (3), 131 (4), 145 (7), 159 (5), 175 (10), 195 (3), 215 (6), 235 (22), 249 (7), 263 (9), 277 (41), 305 (15), 320 (90).

1-[Bis(4-methoxyphenyl)methyl]-3-nitrobenzene (13): Pale yellow solid; m.p. 90–93 °C. ^1H NMR: see ref.[16] ^{13}C NMR: see ref.[16] $C_{21}H_{19}NO_4$ (349.39): calcd. C 72.19, H 5.48, N 4.01, O 18.32; found C 72.16, H 5.44, N 3.97, O 18.29.

1-[Bis(4-methoxyphenyl)methyl]-4-fluorobenzene (14): Yellow solid; m.p. 89–90 °C. ^1H NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 3.82 (2 s, 6 H, CH_3), 5.34 (s, 1 H, Ar_3CH), 6.85–8.01 (m, 8 H, aromatic H) ppm. ^{13}C NMR (200 MHz, $CDCl_3$; Me_4Si): δ = 54.82, 55.71, 114.04, 114.45–115.15 (d, J = 28 Hz, *o*-CH), 129.59, 130.41–130.59 (d, J = 7.2 Hz, *m*-CH) 135.79, 139.25–139.32 (d, J = 2 Hz, *p*-C) 157.99, 157.65–164.15 (d, J = 260 Hz, CF) ppm. $C_{21}H_{19}FO_2$ (322.38): calcd. C 78.24, H 5.94, F 5.89, O 9.93; found: C 78.20, H 5.91, F 5.86, O 9.90. MS: *m*/*z* (%) = 322 (100) [M^+], 53 (6), 77(5), 95 (8), 120 (7), 133 (10), 146 (16), 156 (11), 178 (74), 185 (36), 189 (15), 213 (15), 227 (45), 255 (33), 270 (80).

[1] S. Kobayashi, M. Sugiura, H. Kitagawa, W. L. Lam, *Chem. Rev.* **2002**, *102*, 2227.

[2] S. Kobayashi, *Chem. Lett.* **1991**, 2187.

[3] a) M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, *Tetrahedron Lett.* **2001**, *42*, 3193; b) M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, *Heterocycles* **2001**, *55*, 1599; c) M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, *Eur. J. Org. Chem.* **2002**, 1562; d) M. Curini, F. Epifano, F. Maltese, O. Rosati, *Tetrahedron Lett.* **2002**, *43*, 4895; e) M. Curini, F. Epifano, F. Maltese, O. Rosati, *Synlett* **2003**, 552; f) M. Curini, F. Epifano, M. C. Marcotullio, F. Maltese, *Eur. J. Org. Chem.* **2003**, 1631; g) Curini, F. Epifano, F. Montanari, O. Rosati, S. Taccone, *Synlett* **2004**, 1832; h) M. Curini, F. Epifano, S. Genovese, M. C. Marcotullio, O. Rosati, *Org. Lett.* **2005**, *7*, 1331; i) M. Curini, F. Epifano, S. Genovese, *Tetrahedron Lett.* **2006**, *47*, 4697; j) M. Curini, F. Epifano, S. Genovese, *Tetrahedron Lett.* **2007**, *48*, 2717.

[4] T. W.Greene, P. G. M. Wust, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**, p. 150.

[5] a) R. Aldag, *Photochromism based on dissociation processes*" in *Photochromism: Molecules and Systems* (Eds.: H. Dürr, H. Bouas-Laurent), Elsevier, London, **1990**; b) M. Irie, *J. Am. Chem. Soc.* **1983**, *105*, 2078.

[6] a) P. Rys, H. Zollinger, *Fundamentals of the Chemistry and Application of Dyes*, Wiley-Interscience, New York, **1972**; b) R. Muthyala, A. R. Katritzky, X. Lan, *Dyes Pigm.* **1994**, *25*, 303.

[7] a) M. S. Shchepinov, V. A. Korshun, *Chem. Soc. Rev.* **2003**, *32*,170; b) D. F. Duxbury, *Chem. Rev.* **1993**, *93*, 381; c) R. Schnitzer, F. Hawking, *Experimental Chemotherapy*, Academic Press, New York, **1963**, vol. 1.

[8] N. Mibu, K. Sumoto, *Chem. Pharm. Bull.* **2000**, *48*, 1810.

[9] A. R. Katritzky, L. Xie, W. Fan, *J. Org. Chem.* **1993**, *58*, 4376.

[10] For reviews, see: a) G. Dyker, *Angew. Chem.* **2000**, *112*, 4407; *Angew. Chem. Int. Ed.* **2000**, *39*, 4237; b) A. S. K. Hashmi, *Gold Bull.* **2003**, *36*, 3; c) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51; d) A. Arcadi, S. D. Guiseppe, *Curr. Org. Chem.* **2004**, *8*, 795; e) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387; f) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; g) A. S. K. Hashmi, L. Schwarz, P. Rubenbauer, M. C. Blanco, *Adv. Synth. Catal.* **2006**, *348*, 705–708.

[11] Z. Li, Z. Duan, J. Koung, H. Yu, *Tetrahedron* **2008**, *64*, 1924–1930 and references cited herein.

[12] N. Vijay, K. G. Abhilash, N. Vidya, *Org. Lett.* **2005**, *7*, 5857–5859 and references cited herein.

[13] M. Fieser, *Reagents for Organic Synthesis*, Wiley-Interscience, New York, **1989**, vol. 14, p. 188.

[14] a) S. C. Cagieva, T. A. Sukhova, D. V. Savinov, V. A. Tuskaev, K. A. Lyssenko, N. M. Bravaya, N. Belokon, B. M. Bulychew, *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 1794–1802.

[15] N. Vijay, K. G. Abhilash, *Synthesis* **2006**, 3647–3653 and references cited herein.

[16] S. Podder, U. K. Roy, S. J. Roy, *J. Org. Chem.* **2007**, *72*, 3103–3105 and references cited herein.

[17] P. Ceccherelli, M. Curini, M. C. Marcotullio, O. Rosati, E. Wenkert, *J. Org. Chem.* **1991**, *56*, 7065.

Received: November 11, 2008
Published Online: January 29, 2009

