Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2006, **16(4)**, 215–218

Mendeleev Communications

EWG-containing thiophene- and 2-thiolene-1,1-dioxides as promising electrophiles for organic synthesis

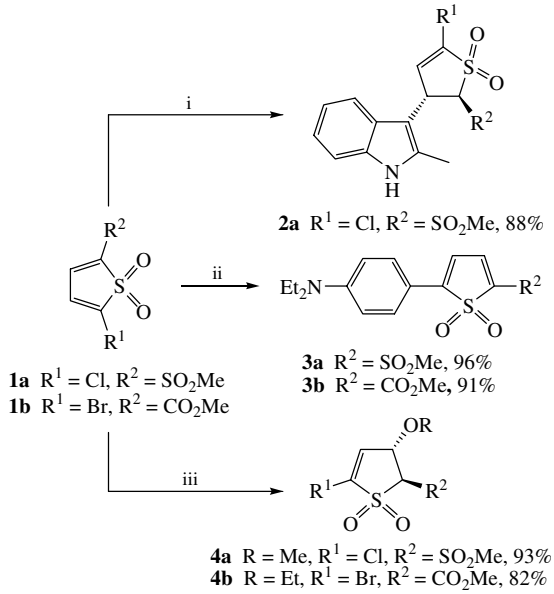
Andrew M. Moiseev, Elizabeth S. Balenkova and Valentine G. Nenajdenko*

Department of Chemistry, M. V. Lomonosov Moscow State University, 119992 Moscow, Russian Federation. Fax: +7 495 932 8846; e-mail: nen@acylium.chem.msu.ru

DOI: 10.1070/MC2006v016n04ABEH002355

The reactions of thiophene- and 2-thiolene-1,1-dioxides bearing electron-withdrawing groups (EWGs) with C-, O-, and S-nucleophiles lead to regio- and stereo-selective formation of Michael adducts in high yields.

Thiophene-1,1-dioxides and their derivatives have been broadly investigated in organic,[1] bioorganic[2] and materials[3] chemistry. On the contrary, EWG-bearing thiophene-1,1-dioxides are poorly investigated substances of this class. Recently, we developed an effective and convenient procedure for the synthesis of substituted thiophene-1,1-dioxides[4] and reported several EWG-containing derivatives, which possess extremely high dienophilic activity in Diels–Alder reactions.[5] As the extension of the study, we have examined some EWG-activated thiophene-1,1-dioxides and 2-thiolene-1,1-dioxides in the reactions with C-, O- and S-nucleophiles.[†]



Scheme 1 *Reagents and conditions*: i, 2-methylindole, THF, room temperature, 2 h; ii, *N*,*N*-diethylaniline, THF, room temperature, 3 h; iii, ROH, THF, room temperature, 30 min.

Based on our previous discovery, we assumed the highly electrophilic nature of these thiophene-1,1-dioxides; thus, substrates **1a** and **1b** were chosen for the further investigation. We found that **1a** and **1b** easily react with weak carbon nucleophiles such as 2-methylindole and *N*,*N*-diethylaniline (Scheme 1).

† NMR spectra were recorded on a Bruker-400 MHz FT spectrometer using $CDCl_3$ as the solvent unless otherwise specified. The chemical shifts are given in δ scale with tetramethylsilane as internal standard. Analytical TLC was performed on Merck silica gel plates (60 F-254). Initial thiophene-1,1-dioxides **1a–c** were synthesised by oxidation of corresponding thiophenes.[4(a),(b)]. Adduct **5** was prepared according to the developed procedure.[5(a)]

General procedure for Michael reaction. Michael reaction of **1a**,**b** and **5** (1 mmol) with nucleophile (1 mmol) was carried out in anhydrous THF (5 ml). For initial adduct **5** reaction mixture was stirred in the presence of flame-dried KF or CsF (1 mmol). All procedures were conducted at room temperature except mono-addition of the diethylmalonate to **5** which was carried out at 0–5 °C. The end of the reaction was detected by TLC. After the reaction was complete, the reaction mixture was passed through a short column of silica gel eluting with hexane–EtOAc (2:1). The eluent was evaporated *in vacuo* to give the pure Michael adduct.

2a: yield 88%, reddish oil. ^{1}H NMR, δ: 2.42 (s, 3H, Me), 3.12 (s, 3H, $MeSO_2$), 4.96 (dd, 1H, C^{3}H, *J* 3.1, 5.3, 8.6 Hz), 5.06 (d, 1H, C^{2}H, *J* 5.3 Hz), 7.04 (d, 1H, C^{4}H, *J* 3.1 Hz), 7.05–7.14 (m, 2H, arom.), 7.34–7.37 (m, 2H, arom.). ^{13}C NMR, δ: 41.72, 58.56, 73.85, 78.48, 130.94, 136.58. Found (%): C, 46.49, H, 3.87. Calc. for $C_{14}H_{14}ClNO_4S_2$ (%): C, 46.73, H, 3.92.

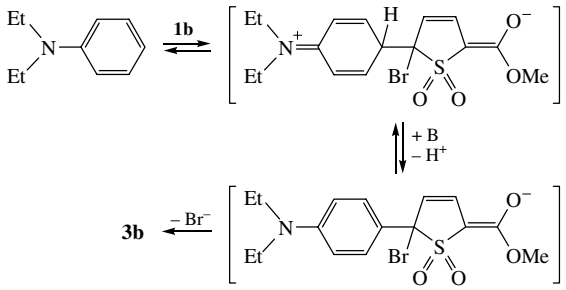
3a: yield 96%, red oil. ^{1}H NMR, δ: 1.26 (t, 6H, 2*Me*CH_2, *J* 7.1 Hz), 3.10 (s, 3H, $MeSO_2$), 3.46–3.50 (m, 4H, 2MeCH_2), 6.58 (d, 1H, C^{5}H, *J* 5.0 Hz), 6.68 (d, 2H, arom., *J* 8.9 Hz), 7.60 (d, 1H, C^{2}H, *J* 5.0 Hz), 7.65 (d, 2H, arom., *J* 8.9 Hz). ^{13}C NMR, δ: 13.22, 44.45, 43.77, 109.88, 114.62, 128.81, 135.60, 139.05, 143.57, 148.42, 149.33. Found (%): C, 52.46, H, 5.49. Calc. for $C_{15}H_{19}NO_4S_2$ (%): C, 52.76, H, 5.61.

3b: yield 91%, red oil. ^{1}H NMR, δ: 1.24 (t, 6H, 2*Me*CH_2, *J* 7.1, 14.0 Hz), 3.29 (s, 3H, $MeCO_2$), 3.44–3.49 (m, 4H, 2MeCH_2), 6.60 (d, 1H, C^{5}H, *J* 5.3 Hz), 6.71 (d, 2H, arom., *J* 9.1 Hz), 7.62 (d, 1H, C^{2}H, *J* 5.3 Hz), 7.68 (d, 2H, arom., *J* 9.1 Hz). ^{13}C NMR, δ: 13.24, 44.66, 53.07, 108.58, 116.04, 127.58, 131.09, 132.55, 139.47, 146.22, 148.43, 158.29. Found (%): C, 59.60, H, 5.74. Calc. for $C_{16}H_{19}NO_4S$ (%): C, 59.79, H, 5.96.

4a: yield 93%, yellowish oil. ^{1}H NMR, δ: 3.37 (s, 3H, $MeSO_2$), 3.58 (s, 3H, MeO), 4.53 (d, 1H, C^{2}H, *J* 2.3 Hz), 5.00 (m, 1H, C^{3}H), 6.76 (d, 1H, C^{4}H, *J* 3.5 Hz). ^{13}C NMR, δ: 41.72, 58.56, 73.85, 78.48, 130.94, 136.58. Found (%): C, 27.29, H, 3.61. Calc. for $C_6H_9ClO_5S_2$ (%): C, 27.64, H, 3.48.

4b: yield 82%, yellowish oil. ^{1}H NMR, δ: 1.28 (t, 3H, *Me*CH_2O, *J* 7 Hz), 3.35 (s, 3H, $MeSO_2$), 3.68–3.87 (m, 2H, MeCH_2O), 4.55 (d, 1H, C^{2}H, *J* 2.5 Hz), 5.08 (m, 1H, C^{3}H), 6.76 (d, 1H, C^{4}H, *J* 3.8 Hz). ^{13}C NMR, δ: 41.75, 58.60, 73.81, 78.45, 130.91, 136.61. Found (%): C, 29.99, H, 4.02. Calc. for $C_7H_{11}ClO_5S_2$ (%): C, 30.60, H, 4.04.

Thiophenedioxides exhibit dual reactivity in the addition of the nucleophiles. For instance, thiophenedioxide **1a** serves as a Michael acceptor in the reaction with 2-methylindole giving rise to *trans*-adduct **2a** regioselectively and in high yield. Meanwhile, unexpected results were obtained in the reaction of **1a** or **1b** with *N*,*N*-diethylaniline. Based on spectroscopic data, products **3a** and **3b** can be regarded as the products of S_EAr reaction of *N*,*N*-diethylaniline with electrophiles **1a** and **1b**. These unusual results have never been observed in the chemistry of thiophene-1,1-dioxides; on the contrary, a Michael-type reaction for this nucleophile is usually anticipated. The most reasonable mechanism for this substitution implies C–C couplings of the S_NAr–S_EAr type, a class of reactions, which requires a very strong reactivity of electrophilic partner and is very difficult to achieve in the benzene series.[6] Thus, the result of the reaction can be best explained as described in Scheme 2 with reference to the reaction of **1b** with *N*,*N*-diethylaniline. We assume the formation of a zwitterionic Wheland-Meisenheimer intermediate. Base-catalysed proton elimination followed by rearomatization and facile loss of a halogen ion results in substitution product **3b**.[6a]



Scheme 2

This mechanistic assumption allows us to clarify differences between the reaction pathways of 2-methylindole and *N*,*N*-diethylaniline. The latter could act as a base (unlike 2-methylindole) and participate in the rate-limiting step of the substitution reaction. Whereas *N*,*N*-diethylaniline serves as a nucleophilic agent and a base simultaneously, the 2-methylindole does not possess required basicity and, thus, undergoes Michael-type reaction.

Next, we found that the O-nucleophiles MeOH and EtOH reacted with **1a** much more easily at room temperature in THF for 30 min to give regio- and stereoselective corresponding Michael adducts **4a** (93%) and **4b** (82%). Therefore, in examined transformations, the reaction pathway depends on the structure of thiophenedioxide, as well as on the nucleophilic agent.

Finally, the reactions of thiolen-1,1-dioxide **5** with various nucleophiles were investigated for comparison (Scheme 3).‡ Previously, we found that thiophen-1,1-dioxide **1c** easily forms **5** as the Diels–Alder adduct with 2,3-dimethylbutadiene.[5(a)] The latter adduct represents another example of Michael acceptor. We have now examined the effective route of Diels–Alder reaction followed by Michael addition, which leads to complex multifunctional molecules starting from one thiophen-1,1-dioxide.

Product **5** does not react with alcohols and 2-methylindole even under elevated temperatures in contrast to starting thiophene-1,1-dioxides. However, more nucleophilic *p*-methoxythiophenol easily gives product **7** within several minutes at room temperature in a nearly quantitative yield. The Michael adduct is formed as a single diastereomer, one of eight possible. Thus, the results lead us to the conclusion that Michael reactions with C- and O-nucleophiles need appropriate activation. Recently, we have shown that KF may act as a selective and mild base in activation of CH acids.[7] In the presence of KF, ethanol and isopropanol form corresponding *trans* adducts in high yields. Note that the reaction of **5** proceeds with competitive formation of by-product **6** due to elimination of the $MeSO_2$ group and subsequent addition of the methylsulfinyl anion to the activated double bond (Scheme 3). Previously, we observed such a rearrangement[6(b)] at a higher temperature; however, in the presence of KF, product **6** is formed even at room temperature. Other organic bases,

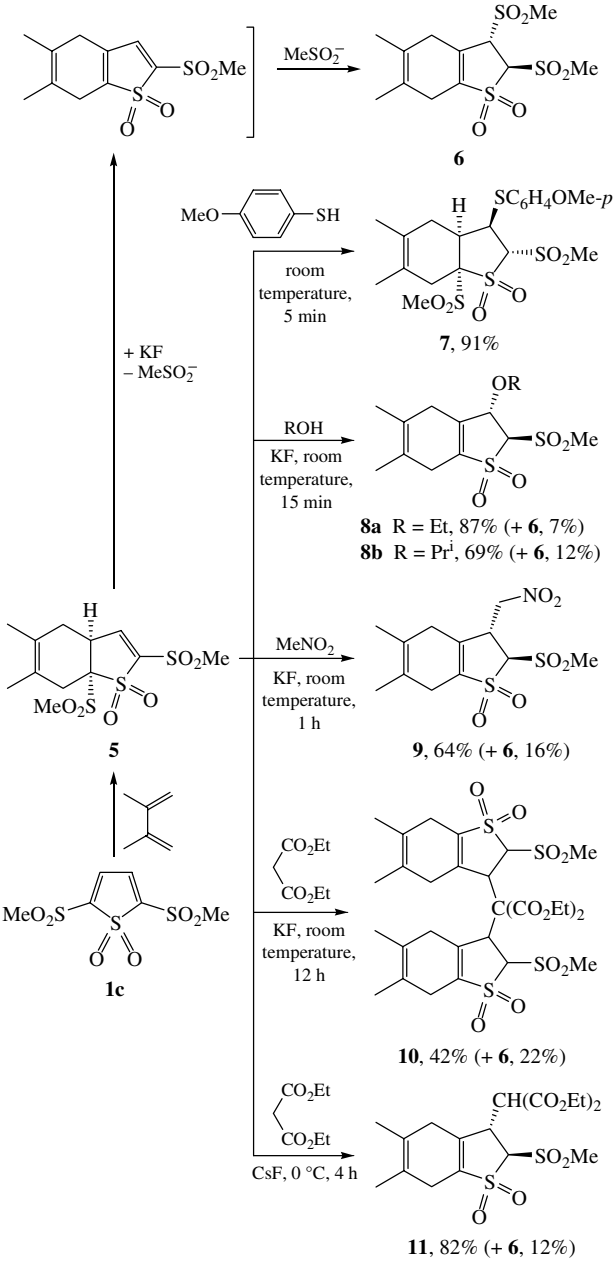
such as pyridine, triethylamine and 1,8-diazobicyclo[5.4.0]-undec-7-ene (DBU), as well as inorganic bases, did not provide desirable selectivity in the formation of a target Michael adduct. In the presence of these bases, the reaction led exclusively to the formation of product **6**.

We found that KF also provides the mild activation of CH acids such as nitromethane and diethylmalonate. The reaction, similarly to one with alcohols, leads to stereoselective formation of Michael *trans* adducts and simultaneous elimination of the $MeSO_2$ group. The remarkable result was obtained in case of diethylmalonate. Product **10** of double addition is formed regardless of the amount of a base and/or a nucleophile. However, the use of CsF at low temperatures allowed us to obtain mono adduct **11** selectively.

The assignment of the substitution spatial orientation in all of the prepared Michael adducts was carried out by analysing NOESY connectivities, as well as long-range hetero-correlation methods. The only one stereoisomer was observed for adduct **7** having four asymmetric centres. The *cis*-ring junction resulted from the rule of the Diels–Alder reaction.[5(*a*)]

The analysis of the molecular models revealed a favourable dihedral angle of *ca.* 180° for the protons H(C^2) and H(C^3). This fact is corroborated by the unexpectedly high value of their vicinal coupling $^3J_{HH}$ 11.3 Hz. Unlikely, this coupling in the other *trans*-Michael adducts bearing less bulkier groups ranges around 2 Hz. These assignments are supported by the X-ray structure determination of **6**.[5(*b*)] It should be noted that the presence of two EWGs at C^2 and C^3 also decreases $^3J_{HH}$ coupling between corresponding protons. Therefore, we observed relatively low $^3J_{HH}$ in most adducts comparing with this coupling in **7**.

In conclusion, we showed that both functionalised thiophene-1,1-dioxides and thiolene-1,1-dioxide **5** undergo the reactions with a variety of nucleophiles. Thiophenedioxides exhibit dual reactivity towards C-nucleophiles: S_NAr carbon–carbon couplings or Michael reaction. A number of transformations including stepwise introduction of carbocyclic moiety followed by functionalization regio- and stereoselectively giving rise to corresponding adducts in high yields.



Scheme 3

This work was supported by the Russian Foundation for Basic Research (grant no. 06-03-32510-a) and the Russian Science Support Foundation.

References

1 (*a*) M. S. Raasch, *J. Org. Chem.*, 1980, **45**, 856; (*b*) S. Gronowitz, in *The Chemistry of Heterocyclic Compounds: a Series of Monographs*, Wiley, New York, 1985, vol. 44, p. 571; (*c*) J. Nakayama and Y. Sugihara, in *Topics in Current Chemistry*, Springer, Berlin, Heidelberg, 1999, vol. 205, p. 131.

2 (*a*) A. M. Alonso, R. H. Horcajada, M. Motevalli, J. H. P. Utley and P. B. Weatt, *Org. Biomol. Chem.*, 2005, **3**, 2842; (*b*) A. Innocenti, R. Villar, V. Martinez-Merino, M. J. Gil, A. Scozzafava, D. Vullo and C. T. Supuran, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4872.

3 (*a*) G. Barbarella, O. Pudova, C. Arbizzani, M. Mastragostino and A. Bongini, *J. Org. Chem.*, 1998, **63**, 1742; (*b*) M. Pasini, S. Destri, W. Porzio, C. Botta and U. Giovanella, *J. Mater. Chem.*, 2003, **13**, 807.

‡ **7**: yield 91%, colourless solid, mp 189 °C. ^{1}H NMR, δ: 1.62 (s, 3H, Me), 1.73 (s, 3H, Me), 2.37 (m, 1H, CH_2, C^4H_β), 2.66 (m, 1H, CH_2, C^7H_β), 2.78 (m, 1H, CH_2, C^4H_α), 2.86 (m, 1H, CH_2, C^7H_α), 3.05 (m, 1H, C^{3a}H), 3.08 (s, 3H, $MeSO_2$), 3.30 (s, 3H, $MeSO_2C^1$), 3.36 (t, 1H, CH–S, *J* 11.3, 22.2 Hz), 3.84 (s, 3H, MeO), 4.47 (d, 1H, C*H*–SO_2Me, *J* 11.3 Hz), 6.93 (d, 2H, arom., *J* 8.9 Hz), 7.55 (d, 2H, arom., *J* 8.9 Hz). ^{13}C NMR, δ: 18.57, 19.41, 28.62, 29.41, 38.00, 39.17, 43.02, 45.64, 55.40, 79.55, 84.68, 115.37, 118.59, 122.81, 124.43, 137.98, 161.37. Found (%): C, 46.10, H, 5.42. Calc. for $C_{19}H_{26}O_7S_4$ (%): C, 46.13, H, 5.30.

8a: yield 87%, colourless oil. ^{1}H NMR, δ: 1.26 (t, 3H, *Me*CH_2, *J* 7.0 Hz), 1.73 (s, 3H, Me), 1.75 (s, 3H, Me), 2.74–2.79 (m, 2H, CH_2), 2.99–3.12 (m, 2H, CH_2), 3.35 (s, 3H, $MeSO_2$), 3.69 (m, 1H, MeC*H*), 3.86 (m, 1H, CH_3C*H*H), 4.39 (d, 1H, CH, *J* 2.0 Hz), 4.89 (br. s, 1H, CH). ^{13}C NMR δ: 18.55, 19.39, 28.66, 29.48, 38.04, 39.22, 43.02, 45.67, 55.40, 79.66, 115.41, 138.00, 161.41. Found (%): C, 48.69, H, 6.31. Calc. for $C_{13}H_{20}O_5S_2$ (%): C, 48.73, H, 6.29.

8b: yield 69%, colourless oil. ^{1}H NMR, δ: 1.22 (d, 3H, 2CH*Me*, *J* 6.1 Hz), 1.24 (d, 3H, 2CH*Me*, *J* 5.9 Hz), 1.72 (s, 3H, Me), 1.74 (s, 3H, Me), 2.67–2.76 (m, 2H, CH_2), 2.97–3.12 (m, 2H, CH_2), 3.35 (s, 3H, $MeSO_2$), 4.04 (m, 1H, C*H*Me), 4.35 (d, 1H, CH, *J* 2.0 Hz), 4.95 (br. s, 1H, CH). ^{13}C NMR, δ: 18.37, 18.42, 21.24, 22.90, 26.27, 32.56, 41.53, 72.80, 73.92, 80.75, 120.88, 121.76, 135.77, 142.44. Found (%): C, 50.16, H, 6.54. Calc. for $C_{14}H_{22}O_5S_2$ (%): C, 50.28, H, 6.63.

9: yield 82%, yellowish solid, mp 211 °C. ^{1}H NMR ([$^2H_6$]acetone) δ: 1.72 (s, 3H, Me), 1.76 (s, 3H, Me), 2.81–3.12 (m, 4H, CH_2), 3.19 (s, 3H, $MeSO_2$), 4.21–4.29 (m, 1H, CH_2NO_2), 4.36 (br. s, 1H, CH), 4.50–4.53 (m, 1H, CH_2NO_2), 5.47 (d, 1H, CH, *J* 2.0 Hz). ^{13}C NMR ([$^2H_6$]acetone) δ: 19.10, 19.85, 29.58, 40.38, 42.61, 55.89, 72.29, 80.01, 118.47, 124.91, 129.05, 130.10. Found (%): C, 42.78, H, 5.22. Calc. for $C_{12}H_{17}NO_6S_2$ (%): C, 42.97, H, 5.11.

10: yield 42%, yellow oil. ^{1}H NMR ([$^2H_6$]acetone) δ: 1.20 (t, 6H, *Me*CH_2, *J* 7.0 Hz), 1.73 (s, 6H, Me), 1.76 (s, 6H, Me), 2.92–3.08 (m, 8H, CH_2), 3.33 (s, 6H, $MeSO_2$), 3.65–3.74 (m, 2H, MeCH_2), 3.80–3.88 (m, 2H, MeCH_2), 4.93–4.95 (m, 4H, CH). ^{13}C NMR ([$^2H_6$]acetone) δ: 13.90, 19.16, 19.88, 29.97, 42.40, 42.91, 49.33, 61.63, 66.01, 80.70, 118.48, 125.53, 127.32, 130.57, 158.43, 159.47. Found (%): C, 49.10, H, 5.61. Calc. for $C_{29}H_{40}O_{12}S_4$ (%): C, 49.13, H, 5.69.

11: yield 82%, colourless solid, mp 163 °C. ^{1}H NMR, δ: 1.27–1.31 (m, 6H, 2*Me*CH_2), 1.69 (s, 3H, Me), 1.73 (s, 3H, Me), 2.84–2.98 (m, 4H, CH_2), 3.33 (s, 3H, $MeSO_2$), 3.97 (d, 1H, CH, *J* 3.8 Hz), 4.07 (m, 1H, CH), 4.21–4.31 (m, 2MeCH_2), 4.80 (d, 1H, CH, *J* 4.3 Hz). ^{13}C NMR, δ: 13.84, 18.30, 18.43, 26.36, 30.90, 34.04, 40.90, 41.07, 52.25, 62.49, 62.61, 76.34, 120.90, 121.46, 135.26, 141.26, 166.32, 166.47. Found (%): C, 49.71, H, 6.12. Calc. for $C_{18}H_{26}O_8S_2$ (%): C, 49.75, H, 6.03.

4 (*a*) V. G. Nenajdenko, A. E. Gavryushin and E. S. Balenkova, *Tetrahedron Lett*., 2001, **42**, 4397; (*b*) V. G. Nenajdenko, A. M. Moiseev and E. S. Balenkova, *Izv. Akad. Nauk., Ser. Khim*., 2004, 2144 (*Russ. Chem. Bull., Int. Ed*., 2004, **53**, 2241).

5 (*a*) V. G. Nenajdenko, A. M. Moiseev and E. S. Balenkova, *Tetrahedron*, 2005, **61**, 10880; (*b*) V. G. Nenajdenko, A. M. Moiseev and E. S. Balenkova, *Izv. Akad. Nauk. Ser. Khim*., 2005, 2117 (*Russ. Chem. Bull., Int. Ed*., 2005, **54**, 2182); (*c*) V. G. Nenajdenko, A. M. Moiseev and E. S. Balenkova, *Tetrahedron*, 2006, **61**, 4139.

6 (*a*) F. Effenberger, *Acc. Chem. Res*., 1989, **22**, 27; (*b*) S. Kurbatov, P. Rodriguez-Daftonte, R. Goumont and F. Terrier, *Chem. Commun*., 2003, 2150.

7 (*a*) V. G. Nenajdenko, S. V. Druzhinin and E. S. Balenkova, *Tetrahedron Lett*., 2005, **46**, 8853; (*b*) A. V. Sanin, V. G. Nenajdenko, A. L. Krasovskii, A. V. Churakov, J. A. K. Howard and E. S. Balenkova, *Zh. Org. Khim*., 1997, **33**, 236 (*Russ. J. Org. Chem*., 1997, **33**, 205).

Received: 14th March 2006; Com. 06/2700