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SYNTHESIS OF HETEROCYCLES ON THE BASIS OF ARYLATION PRODUCTS OF UNSATURATED COMPOUNDS. 19.* ARYLATION OF 2-ACETYLTHIOPHENE AND THE SYNTHESIS OF 2-(5-ARYL-2-THIENYL)-4-QUINOLINECARBOXYLIC ACIDS

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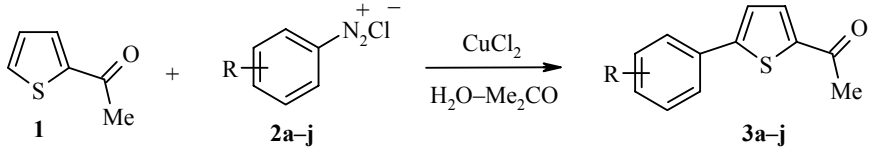
The reaction of 2-acetylthiophene with acetylthiophene with arenediazonium chlorides in the presence of cupric chloride as catalyst gives 2-acetyl-5-arylthiophenes. These products react with 5-chloro- and 5-bromoisatins to give 6-chloro- and 6-bromo-substituted 2-(5-aryl-2-thienyl)-4-quinolinecarboxylic acids.

Keywords: 2-acetyl-5-arylthiophenes, 2-acetylthiophene, 4-quinolinecarboxylic acid derivatives, arylation, Meerwein reaction, Pfitzinger reaction.

Some heteroaromatic compounds are arylated by arenediazonium compounds under conditions of the Meerwein reaction [2-5]. Furan derivatives (especially furfural) have been studied extensively in this reaction since they have proved to be the most reactive [5-8]. Various workers [9-12] have described the arylation of 2-thiophenecarbaldehyde by arenediazonium salts. Shridhar et al. [13] have demonstrated the use of 2-acetylthiophene in this reaction. 2-Acetyl-5-arylthiophenes have usually been obtained by other methods, namely, by acylation of 2-arylthiophenes [14] or by the palladium-catalyzed arylation of 2-acetylthiophene using various reagents [15-18]. We should note that, in the latter case, the reactions do not always proceed



a R = 4-Me**, b** R = 4-F, **c** R = 2-Cl, **d** R = 4-Cl, **e** R = 4-Br, **f** R = 3-NO_2, **g** R = 4-NO_2, **h** R = 3-CF_3, **i** R = 2,5-Cl_2, **j** R = 2-Cl-5-CF_3

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selectively [19]. On the other hand, the preparative synthesis of 2-acetyl-5-arylthiophenes using the Meerwein reaction is attractive since it does not require the use of not readily available starting compounds and catalysts.

With this in mind, we have carried out a detailed study of the arylation of 2-acetylthiophene **1** by arenediazonium chlorides **2a-j**. This reaction proceeds in the presence of cupric chloride as catalyst at room temperature to give 5-aryl-2-acetylthiophenes **3a-j** (Tables 1 and 2).

The yields of acetylthiophenes **3** are usually in the range 30-55%, which indicates that acetylthiophene is somewhat less reactive than acetylfuran in this reaction [20]. Moderate yields of 30-40% are characteristic for the Meerwein reaction [2, 5]. However, the starting reagents for the preparation of acetylthiophenes **3** in this case are readily available aromatic amines and 2-acetylthiophene.

TABLE 1. Characteristics of Products **3a-j** and **5a-n**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield %
		C	H	N		
3a	$C_{13}H_{12}OS$	71.87 / 72.19	5.43 / 5.59		115-116	20
3b	$C_{12}H_9FOS$	65.31 / 65.44	4.03 / 4.12		97-98	41
3c	$C_{12}H_9ClOS$	60.46 / 60.89	3.76 / 3.83		67-68	47
3d	$C_{12}H_9ClOS$	60.74 / 60.89	3.72 / 3.83		114-115	30
3e	$C_{12}H_9BrOS$	51.04 / 51.26	3.19 / 3.23		140-142	33
3f	$C_{12}H_9NO_3S$	58.21 / 58.29	3.54 / 3.67	5.51 / 5.66	148-149	40
3g	$C_{12}H_9NO_3S$	58.18 / 58.29	3.49 / 3.67	5.83 / 5.66	153-154	55
3h	$C_{13}H_9F_3OS$	57.89 / 57.77	3.28 / 3.36		87-88	29
3i	$C_{12}H_8Cl_2OS$	52.91 / 53.15	3.05 / 2.97		112-113	44
3j	$C_{13}H_8ClF_3OS$	51.37 / 51.24	2.49 / 2.65		74-75	49
5a	$C_{21}H_{14}ClNO_2S$	66.22 / 66.40	3.54 / 3.71	3.53 / 3.69	268-269	74
5b	$C_{21}H_{14}BrNO_2S$	59.17 / 59.44	3.12 / 3.33	3.16 / 3.30	283-284	55
5c	$C_{20}H_{11}ClFNO_2S$	62.37 / 62.59	2.75 / 2.89	3.49 / 3.65	284-285	82
5d	$C_{20}H_{11}BrFNO_2S$	55.98 / 56.09	2.45 / 2.59	3.14 / 3.27	294-295	79
5e	$C_{20}H_{11}Cl_2NO_2S$	59.84 / 60.01	2.71 / 2.77	3.38 / 3.50	258-259	83
5f	$C_{20}H_{11}BrClNO_2S$	53.84 / 54.01	2.42 / 2.49	3.06 / 3.15	272-273	71
5g	$C_{20}H_{11}Cl_2NO_2S$	59.88 / 60.01	2.59 / 2.77	3.33 / 3.50	283-284	78
5h	$C_{20}H_{11}BrClNO_2S$	53.98 / 54.01	2.37 / 2.49	3.02 / 3.15	292-293	74
5i	$C_{21}H_{11}ClF_3NO_2S$	58.00 / 58.14	2.43 / 2.56	3.07 / 3.23	253-254	76
5j	$C_{21}H_{11}BrF_3NO_2S$	52.63 / 52.74	2.30 / 2.32	2.86 / 2.93	287-288	69
5k	$C_{20}H_{10}Cl_3NO_2S$	55.04 / 55.26	2.41 / 2.32	3.01 / 3.22	245-246	77
5l	$C_{20}H_{10}BrCl_2NO_2S$	49.94 / 50.13	1.78 / 2.10	3.10 / 2.92	253-254	69
5m	$C_{21}H_{10}Cl_2F_3NO_2S$	53.78 / 53.86	1.98 / 2.15	3.05 / 2.99	290-291	83
5n	$C_{21}H_{10}BrClF_3NO_2S$	49.02 / 49.19	1.80 / 1.97	2.59 / 2.73	> 300	67

TABLE 2. ^{1}H NMR Spectra of **3a-j** and **5a-n**

Com-pound	Chemical shifts, δ, ppm, (*J*, Hz)*
1	2
3a	2.39 (3H, s, CH_3); 2.55 (3H, s, CH_3); 7.24 (2H, d, *J* = 8.0, C_6H_4); 7.29 (1H, d, *J* = 4.0, thiophene);7.52 (2H, d, *J* = 8.0, C_6H_4); 7.66 (1H, d, *J* = 4.0, thiophene)
3b	2.53 (3H, s, CH_3); 7.11 (2H, t, *J* = 8.4, C_6H_4); 7.26 (1H, d, *J* = 4.2, thiophene); 7.57 (2H, dd, *J* = 8.4 and *J* = 5.2, C_6H_4); 7.66 (1H, d, *J* = 4.2, thiophene)
3c	2.54 (3H, s, CH_3); 7.43 (1H, t, *J* = 7.8, C_6H_4); 7.45-7.55 (2H, m, thiophene + C_6H_4); 7.74 (1H, d, *J* = 7.8, C_6H_4); 7.79 (1H, d, *J* = 4.0, thiophene); 7.94 (1H, d, *J* = 7.8, C_6H_4)
3d	2.53 (3H, s, CH_3); 7.45 (2H, d, *J* = 8.4, C_6H_4); 7.54 (1H, d, *J* = 4.0, thiophene); 7.72 (2H, d, *J* = 8.4, C_6H_4); 7.83 (1H, d, *J* = 8.4, thiophene)
3e	2.52 (3H, s, CH_3); 7.41 (2H, d, *J* = 8.4, C_6H_4); 7.57-7.64 (3H, m, thiophene + C_6H_4); 7.87 (1H, d, *J* = 4.4, thiophene)
3f	2.56 (3H, s, CH_3); 7.44 (1H, d, *J* = 4.0, thiophene); 7.62 (1H, t, *J* = 7.8, C_6H_4); 7.67 (1H, d, *J* = 4.0, thiophene); 7.96 (1H, d, *J* = 7.8, C_6H_4); 8.17 (1H, d, *J* = 7.8, C_6H_4); 8.40 (1H, s, C_6H_4)
3g	2.56 (3H, s, CH_3); 7.78 (1H, d, *J* = 3.8, H-4 thiophene); 7.91 (1H, d, *J* = 3.8, H-3 thiophene); 7.99 (2H, d, *J* = 8.8, C_6H_4); 8.26 (2H, d, *J* = 8.8, C_6H_4)
3h	2.54 (3H, s, CH_3); 7.60-7.82 (4H, m, thiophene + C_6H_4); 7.84 (1H, d, *J* = 4.2, thiophene); 8.05 (1H, d, *J* = 2.0, C_6H_4)
3i	2.52 (3H, s, CH_3); 7.47 (1H, d, *J* = 8.4, C_6H_3); 7.56 (1H, d, *J* = 4.0, thiophene); 7.74 (1H, dd, *J* = 8.4 and *J* = 2.0, C_6H_3); 7.97 (1H, d, *J* = 4.0, thiophene); 8.08 (1H, d, *J* = 2.0, C_6H_3)
3j	2.53 (3H, s, CH_3); 7.48 (1H, d, *J* = 4.4, thiophene); 7.65-7.79 (3H, m, thiophene + C_6H_3); 8.03 (1H, d, *J* = 2.0, C_6H_3)
5a	2.38 (3H, s, CH_3); 7.23 (2H, d, *J* = 8.0, C_6H_3); 7.49 (1H, d, *J* = 3.9, H-4 thiophene); 7.61 (2H, d, *J* = 8.0, C_6H_4); 7.70 (1H, dd, *J* = 2.4 and *J* = 8.8, H-7 quinoline); 7.96-8.04 (2H, m, H-3 thiophene + H-8 quinoline); 8.47 (1H, s, H-3 quinoline); 8.84 (1H, d, *J* = 2.4, H-5 quinoline)
5b	2.38 (3H, s, CH_3); 7.24 (2H, d, *J* = 8.0, C_6H_3); 7.47 (1H, d, *J* = 4.0, H-4 thiophene); 7.61 (2H, d, *J* = 8.0, C_6H_4); 7.84 (1H, dd, *J* = 2.0 and *J* = 8.8, H-7 quinoline); 7.93 (1H, d, *J* = 8.8, H-8 quinoline); 7.96 (1H, d, *J* = 4.0, H-3 thiophene); 8.43 (1H, s, H-3 quinoline); 8.95 (1H, d, *J* = 2.0, H-5 quinoline)
5c	7.13 (2H, t, *J* = 8.8, C_6H_4); 7.39 (1H, d, *J* = 3.9, H-4 thiophene); 7.66 (1H, dd, *J* = 2.0 and *J* = 8.8, H-7 quinoline); 7.69-7.73 (2H, m, C_6H_4); 7.87 (1H, d, *J* = 3.9, H-3 thiophene); 7.99 (1H, d, *J* = 8.8, H-8 quinoline); 8.43 (1H, s, H-3 quinoline); 8.84 (1H, s, H-5 quinoline)
5d	7.13 (2H, t, *J* = 7.8, H-3,5 C_6H_4); 7.38 (1H, d, *J* = 3.9, H-4 thiophene); 7.68-7.73 (2H, m, H-2,6 C_6H_4); 7.78 (1H, d, *J* = 8.8, H-7 quinoline); 7.86 (1H, d, *J* = 3.9, H-3 thiophene); 7.92 (1H, d, *J* = 8.8, H-8 quinoline); 8.41 (1H, s, H-3 quinoline); 9.00 (1H, s, H-5 quinoline)
5e	7.34-7.40 (2H, m, C_6H_4); 7.48 (1H, d, *J* = 4.0, H-4 thiophene); 7.54 (1H, dd, *J* =1.2 and *J* = 7.6, C_6H_4); 7.69 (1H, dd, *J* =1.6 and *J* = 7.6, C_6H_4); 7.72 (1H, dd, *J* = 2.4 and *J* = 9.2, H-7 quinoline); 7.98 (1H, d, *J* = 4.0, H-3 thiophene); 8.03 (1H, d, *J* = 9.2, H-8 quinoline); 8.47 (1H, s, H-3 quinoline); 8.81 (1H, d, *J* = 2.4, H-5 quinoline)
5f	7.36-7.40 (2H, m, C_6H_4); 7.47 (1H, d, *J* = 4.0, H-4 thiophene); 7.54 (1H, dd, *J* = 1.2 and *J* = 7.6, C_6H_4); 7.69 (1H, dd, *J* = 1.2 and *J* = 7.6, C_6H_4); 7.83 (1H, dd, *J* = 2.0 and *J* = 9.2, H-7 quinoline); 7.96 (1H, d, *J* = 9.2, H-8 quinoline); 7.99 (1H, d, *J* = 4.0, H-3 thiophene); 8.45 (1H, s, H-3 quinoline); 8.98 (1H, d, *J* = 2.0, H-5 quinoline)
5g	7.37 (2H, d, *J* = 8.4, C_6H_4); 7.45-7.52 (3H, m, H-4 thiophene + C_6H_4); 7.70 (1H, dd, *J* = 1.6 and *J* = 9.2, H-7 quinoline); 7.87 (1H, d, *J* = 3.9, H-3 thiophene); 8.02 (1H, d, *J* = 9.2, H-8 quinoline); 8.45 (1H, s, H-3 quinoline); 8.82 (1H, d, *J* = 1.6, H-5 quinoline)
5h	7.36 (2H, d, *J* = 8.8, C_6H_4); 7.47-7.53 (3H, m, H-4 thiophene + C_6H_4); 7.82 (1H, dd, *J* = 8.8, H-7 quinoline); 7.88 (1H, d, *J* = 3.9, H-3 thiophene); 7.94 (1H, d, *J* = 8.8, H-8 quinoline); 8.41 (1H, s, H-3 quinoline); 9.01 (1H, s, H-5 quinoline)

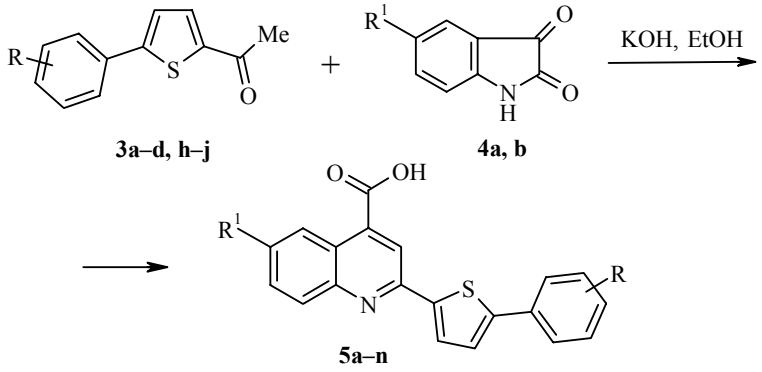
TABLE 2 (continued)

1	2
5i	7.54-7.63 (3H, m, H-4 thiophene + C_6H_4); 7.67 (1H, d, *J* = 8.8, H-7 quinoline); 7.89-7.96 (3H, m, H-3 thiophene + C_6H_4); 8.00 (1H, d, *J* = 8.8, H-8 quinoline); 8.43 (1H, s, H-3 quinoline); 8.85 (1H, s, H-5 quinoline)
5j	7.53-7.62 (3H, m, H-4 thiophene + C_6H_4); 7.80 (1H, d, *J* = 8.8, H-7 quinoline); 7.89-7.99 (4H, m, H-3 thiophene + C_6H_4 + H-8 quinoline); 8.43 (1H, s, H-3 quinoline); 8.99 (1H, s, H-5 quinoline)
5k	7.31 (1H, dd, *J* = 1.6 and *J* = 7.8, C_6H_3); 7.48-7.54 (2H, m, H-4 thiophene + C_6H_3); 7.71 (1H, dd, *J* = 2.0 and *J* = 9.2, H-7 quinoline); 7.91 (1H, d, *J* = 3.9, H-3 thiophene); 8.01-8.07 (2H, m, C_6H_3 + H-8 quinoline); 8.46 (1H, s, H-3 quinoline); 8.84 (1H, d, *J* = 2.0, H-5 quinoline)
5l	7.32 (1H, dd, *J* = 1.2 and *J* = 7.8, C_6H_3); 7.48-7.53 (2H, m, H-4 thiophene + C_6H_3); 7.80 (1H, d, *J* = 8.8, H-7 quinoline); 7.91-7.97 (2H, m, H-3 thiophene + H-8 quinoline); 8.04 (1H, d, *J* = 1.2, C_6H_3); 8.42 (1H, s, H-3 quinoline); 9.02 (1H, s, H-5 quinoline)
5m	7.53 (1H, d, *J* = 3.9, H-4 thiophene); 7.61 (1H, d, *J* = 8.8, H-4 C_6H_3); 7.69 (1H, dd, *J* =2.0 and *J* = 8.8, H-7 quinoline); 7.73 (1H, d, *J* = 8.8, H-3 C_6H_3); 7.92 (1H, s, H-6 C_6H_3); 7.96 (1H, d, *J* = 3.9, H-3 thiophene); 8.05 (1H, d, *J* = 8.8, H-8 quinoline); 8.48 (1H, s, H-3 quinoline); 8.87 (1H, s, H-5 quinoline)
5n	7.53 (1H, d, *J* = 3.9, H-4 thiophene); 7.62 (1H, d, *J* = 7.8, H-4 C_6H_3); 7.74 (1H, d, *J* = 7.8, H-3 C_6H_3); 7.82 (1H, d, *J* = 8.8, H-7 quinoline); 7.92 (1H, s, H-6 C_6H_3); 7.95-8.02 (2H, m, H-3 thiophene + H-8 quinoline); 8.47 (1H, s, H-3 quinoline); 9.04 (1H, s, H-5 quinoline)

*The ^{1}H NMR spectra were obtained in $CDCl_3$ for **3a-c** and **3f** and in DMSO-d_6 for **3d, 3e, 3g-j,** and **5a-n.**

2-Acetyl-5-arylthiophenes are promising reagents for organic synthesis. We have studied the reaction of ketones **3** with 5-chloroisatin **4a** and 5-bromoisatin **4b** under conditions of the Pfitzinger reaction [21, 22]. This reaction of ketones with isatin is the most convenient method for the synthesis of cinchonic (4-quinoline-carboxylic) acids. Many derivatives of cinchonic acid possess biological activity and several such compounds are drugs [22, 23]. Acetylthiophenes **3a-d** and **3h-j** react with isatins **4a**,**b** in ethanol at reflux in the presence of KOH to give 2-(5-aryl-2-thienyl)-4-quinolinecarboxylic acids **5a-n** in high yield.

Thus, we have shown that the arylation of 2-acetylthiophene by arenediazonium salts is a convenient method for the synthesis 2-acetyl-5-arylthiophenes, which may be used for the preparation of synchonic acids with arylthienyl fragments.



5 a R = 4-Me, R^1 = Cl; **b** R = 4-Me, R^1 = Br; **c** R = 4-F, R^1 = Cl; **d** R = 4-F, R^1 = Br; **e** R = 2-Cl, R^1 = Cl; **f** R = 2-Cl, R^1 = Br; **g** R = 4-Cl, R^1 = Cl; **h** R = 4-Cl, R^1 = Br; **i** R = 3-CF_3, R^1 = Cl; **j** R = 3-CF_3, R^1 = Br; **k** R = 2,5-Cl_2, R^1 = Cl; **l** R = 2,5-Cl_2, R^1 = Br; **m** R = 2-Cl-5-CF_3, R^1 = Cl; **n** R = 2-Cl-5-CF_3, R^1 = Br

EXPERIMENTAL

The ^{1}H NMR spectra of thiophenes **3a-c, 3f,** and **5a-n** were taken on a Varian Mercury 400 spectrometer at 400 MHz, while the corresponding spectra of thiophenes **3d, 3e,** and **3g-j** were taken on a Bruker WM-250 spectrometer at 250 MHz using TMS as the internal standard.

2-Acetyl-5-arylthiophenes 3a-j. Aromatic amine (0.1 mol) was dissolved in 20% hydrochloric acid (60 ml), heating when necessary. The solution was cooled to 0-5°C and a solution of $NaNO_2$ (7 g) in water (25 ml) was added dropwise with stirring. After completion of the reaction, the solution of arenediazonium salt **2a-j** was filtered and added dropwise to a mixture of 2-acetylthiophene **1** (12.6 g, 0.1 mol), $CuCl_2 \cdot 2H_2O$ (1 g), and acetone (40 ml). The reaction was carried out at 15-25°C such that nitrogen was released at a moderate rate. After nitrogen evolution ceased, 150 ml water was added to the reaction mixture. The precipitate formed was filtered off and thiophenes **3c-g** and **3i**. If an oil is formed, as in the case of compounds **3a,b,h,j**, it was extracted with chloroform. After distilling off the solvent, the residue was distilled in vacuum and recrystallized from ethanol.

6-Chloro- and 6-Bromo-substituted 2-(5-aryl-2-thienyl)-4-quinolinecarboxylic acids 5a-n. Ethanol (50 ml) and water (5 ml) were added to a mixture of 5-aryl-2-acetylthiophene **3** (4 mmol), 5-chloroisatin **4a** or 5-bromoisatin **4b** (4 mmol), and KOH (0.70 g, 12.5 mmol). The reaction mixture was heated at reflux for 6 h, then poured into water (100 ml), and brought to pH 7 by adding glacial acetic acid. The residue was filtered off and recrystallized from ethanol-DMF.

REFERENCES

1. R. L. Martyak, N. D. Obushak, and V. S. Matiichuk, *Zh. Org. Khim.*, **45**, 555 (2009).
2. A. V. Dombrovskii, *Usp. Khim.*, **53**, 1625 (1984).
3. K. H. Saunders and R. L. Allen, *Aromatic Diazo Compounds*, Edward Arnold, London (1985).
4. H. Zollinger, *Diazo Chemistry. 1. Aromatic and Heteroaromatic Compounds*, VCH, Weinheim, Germany (1994), p. 243.
5. C. S. Rondestvedt, in: *Organic Reactions*, vol. 24, John Wiley, New York-London (1976), p. 225.
6. N. D. Obushak, A. I. Lesyuk, N. I. Ganushchak, G. M. Mel'nik, and Yu. P. Zavalii, *Zh. Org. Khim.*, **22**, 2331 (1986).
7. N. D. Obushak, N. I. Ganushchak, A. I. Lesyuk, L. M. Dzikovskaya, and P. P. Kisilitsa, *Zh. Org. Khim.*, **26**, 873 (1990).
8. A. F. Oleinik, T. I. Vozyakova, G. A. Modnikova, and K. Yu. Novitskii, *Khim. Geterotsikl. Soedin.*, 441 (1972). [*Chem. Heterocycl. Soedin.*, **8**, 402 (1972)].
9. N. D. Obushak, V. S. Matiichuk, and R. Z. Lytvyn, *Khim. Geterotsikl. Soedin.*, 1166 (2008). [*Chem. Heterocycl. Chem.*, **44**, 936 (2008)].
10. R. Frimm, L. Fišera, and J. Kovač, *Collect. Czech. Chem. Commun.*, **38**, 1809 (1973).
11. L. Racane, V. Tralić-Kulenovic, D. W. Boykin, and G. Karminski-Zamola, *Molecules*, **8**, 342 (2003).
12. L. Racane, V. Tralić-Kulenović, G. Karminski-Zamola, and L. Fišer-Jakić, *Monatsh. Chem.*, **126**, 1375 (1995).
13. D. R. Shridhar, C. V. Reddy Sastry, S. C. Chaturvedi, R. Gurumurthy, P. P. Singh, C. Seshagiri Rao, and A. Y. Junnarkar, *Indian J. Chem.*, **23B**, 692 (1984).
14. S. Kotha, K. Chakraborty, and E. Brachmachary, *Synlett*, 1621 (1999).
15. K. M. Lawson Daku, R. F. Newton, S. P. Pearce, J. Vile, and J. M. J. Williams, *Tetrahedron Lett.*, **44**, 5095 (2003).

16. K. Arentsen, S. Caddick, F. G. N. Cloke, A. P. Herring, and P. B. Hitchcock, *Tetrahedron Lett.*, **45**, 3511 (2004).
17. I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, and G. K. Tranmer, *Chem. Eur. J.*, **12**, 4407 (2006).
18. A. Battace, M. Lemhadri, T. Zair, H. Doucet, and M. Santelli, *Adv. Synth. Cat.*, **349**, 2507 (2007).
19. T. Itahara, *J. Org. Chem.*, **50**, 5272 (1985).
20. N. D. Obushak, Yu. I. Gorak, V. S. Matiichuk, and R. Z. Lytvyn, *Zh. Org. Khim.*, **44**, 1712 (2008).
21. M.-G. A. Shvekhgeimer, *Khim. Geterotsikl. Soedin.*, 323 (2004). [*Chem. Heterocycl. Comp.*, **40**, 257 (2004)].
22. J. F. M. da Silva, S. J. Garden, and A. C. Pinto, *J. Braz. Chem. Soc.*, **12**, 273 (2001).
23. M. D. Mashkovskii, *Drugs* [in Russian], Novaya Volna, Moscow (2000).