ISSN 1070-4280, Russian Journal of Organic Chemistry, 2012, Vol. 48, No. 6, pp. 860–863. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © N.N. Romanova, I.I. Rybalko, T.G. Tallo, N.V. Zyk, V.K. Švedas, 2012, published in Zhurnal Organicheskoi Khimii, 2012, Vol. 48, No. 6, pp. 862–865.

SHORT COMMUNICATIONS

Synthesis of Schiff Bases from 3-Amino-3-arylpropionic Acid Esters in Aqueous Medium

N. N. Romanova[a], I. I. Rybalko[a], T. G. Tallo[b], N. V. Zyk[a], and V. K. Švedas[c]

[a] *Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia*
e-mail: romanova@org.chem.msu.ru

[b] *National Institute for Health Development, Tallinn, Estonia*

[c] *Belozerskii Institute of Physicochemical Biology, Moscow State University, Moscow, Russia*

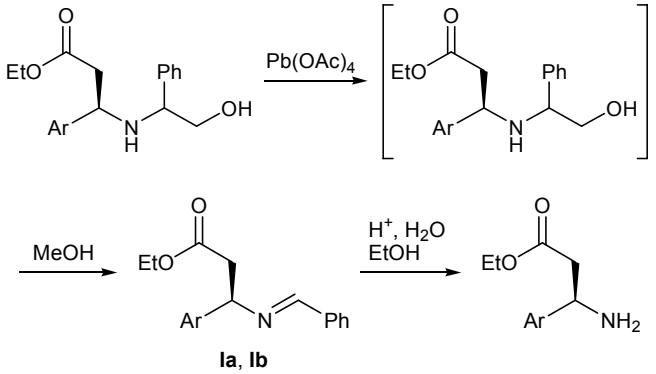
Received January 15, 2012

DOI: 10.1134/S107042801206019X

Schiff bases constitute one of the most thoroughly studied and practically important class of organic compounds. Their biological activity is well known. Some Schiff bases inhibit many enzymes [1–8] and possess bactericidal [9, 10], fungicidal [11, 12], herbicidal, [13] and anticancer activity [14, 15]. Schiff bases had been used in organic synthesis since 1907 when Staudinger reported on their reaction with ketenes [16]. At present Schiff bases are widely used as initial materials in the synthesis of many biologically active compounds, in particular nitrogen-containing heterocycles [17–19] and non-natural amino acids and their derivatives [20, 21]. Exceptional advances in the chemistry of Schiff bases due to their participation in multicomponent reactions should be noted [22].

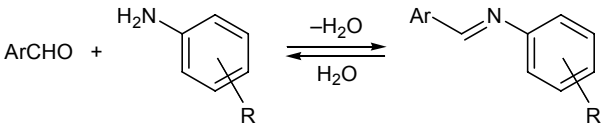
While performing studies in the fields of synthesis and stereochemistry of bioactive β-amino-β-arylpropionic acids [23, 24], we have confronted with the problem related to preparation of the corresponding Schiff bases. Methyl 3-benzylideneamino-3-phenylpropionate was synthesized [25] in anhydrous methylene chloride under argon. Mokhallalati and Pridgen [26] described (but not completely characterized) compounds **Ia** and **Ib** which were prepared in a difficultly realizable way, by oxidative cleavage of 3-aryl-3-[(2-hydroxy-1-phenylethyl)amino]propionic acids esters with lead tetraacetate (Scheme 1).

Scheme 1.



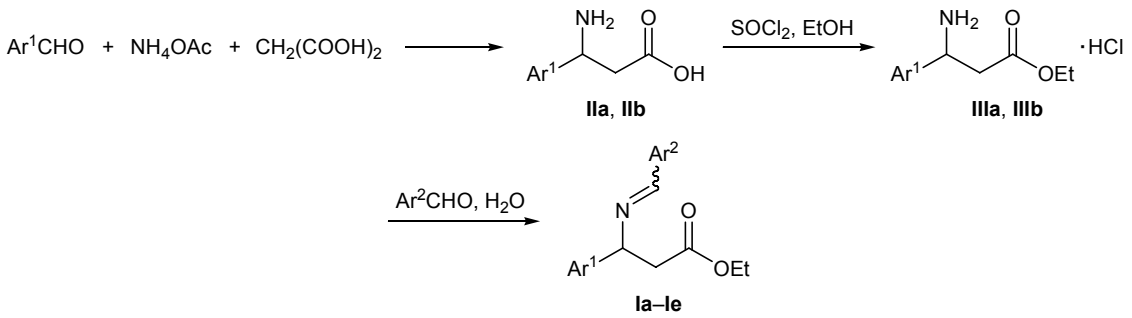
The classical Schiff procedure is based on condensation of carbonyl compounds with primary amines [27] (Scheme 2).

Scheme 2.



The reaction is reversible, and it is usually carried out with simultaneous removal of water as azeotrope or in the presence of molecular sieves [17, 28, 29] to displace the equilibrium. Up-to-date modifications utilize ultrasonic [30] or microwave activation [18, 31, 32]. In the past decade, Schiff condensations were reported to be carried out in aqueous medium [33–35]. Uncommonness of this approach stimulated special study which showed that the use of aqueous medium is possible if the conditions ensure contact of the reactants and the product is insoluble in water; the latter factor is crucial for the displacement of thermodynamic equilibrium [35].

Scheme 3.



$Ar^1 = Ar^2 = Ph$ (**a**); $Ar^1 = 4\text{-}BrC_6H_4$, $Ar^2 = Ph$ (**b**); $Ar^1 = Ph$, $Ar^2 = 4\text{-}BrC_6H_4$ (**c**); $Ar^1 = Ph$, $Ar^2 = 3,4\text{-}(MeO)_2C_6H_3$ (**d**); $Ar^1 = Ph$, $Ar^2 = 2,4\text{-}Cl_2C_6H_3$ (**e**).

In the present communication we describe a convenient procedure for the condensation of aromatic aldehydes with β-amino-β-arylpropionic acid ester hydrochlorides in aqueous medium, which ensures preparation of potentially biologically active Schiff bases **Ia**–**Ie** in good yield (75–87%); the product requires no additional purification.

Initial 3-amino-3-phenyl- and 3-amino-3-(4-bromophenyl)propionic acids **IIa** and **IIb** were synthesized according to Rodionov [36–39] by condensation of the corresponding aromatic aldehydes with malonic acid in the presence of ammonium acetate (Scheme 3); their spectral parameters fully coincided with those reported in the literature. The second product, cinnamic acid, was isolated by pouring the filtrate into a threefold volume of water. Cinnamic acid is insoluble in water, and it separated in 20–40% yield.

Acids **IIa** and **IIb** were subjected to esterification according to modified procedures for the synthesis of ethyl 3-amino-3-phenylpropionate (**IIIa**) [38, 39] and analogous methyl ester (at –10°C [25]) which required purification by recrystallization. Acid **IIa** and **IIb**, 0.1 mol, was dispersed in 75 ml of 96% ethanol, 0.2 mol of thionyl chloride was slowly added to avoid sharp rise in temperature, and the mixture was then heated for 2 h under reflux. When the reaction was complete, the solvent was distilled off on a rotary evaporator, and amino ester hydrochlorides **IIIa** and **IIIb** were additionally precipitated by adding 25 ml of diethyl ether saturated with hydrogen chloride. After filtration, washing with diethyl ether, and drying over P_2O_5 for 2 days we obtained analytically pure hydrochlorides **IIIa** and **IIIb** as white crystals in more than 95% yield.

Schiff bases **Ia**–**Ie** were synthesized by a modified procedure for the preparation of methyl 3-benzylideneamino-3-phenylpropionate which implied the use of anhydrous methylene chloride in a stream of argon [25]. Hydrochloride **IIIa** or **IIIb**, 0.12 mol, was dissolved in water, 0.13 mol of sodium carbonate was added, and 0.1 mol of the corresponding aldehyde was added dropwise (solid aldehyde was added in small portions). The mixture was heated for 2 h at 45–50°C in a flask equipped with a reflux condenser, stirred for 24 h at room temperature, and extracted with methylene chloride (3 × 30 ml). The organic phase was washed with water and dried over $MgSO_4$, and the solvent was removed on a rotary evaporator under reduced pressure to isolate analytically pure Schiff bases **Ia**–**Ie** as mobile oily liquids in 75–87% yield. Compounds **Ia**–**Ie** were characterized by NMR spectra and elemental analyses.

The NMR spectra of **Ia**–**Ie** contained the same signals as in the spectra of the corresponding amino esters, except for the number of aromatic protons due to the presence of an additional aryl group on the nitrogen. In addition, downfield signals from the azomethine proton (δ 8.3–8.9 ppm) and N=CH carbon atom (δ_C 157.07–161.96) were observed. Some signals in the ^{1}H NMR spectra of all Schiff bases **Ia**–**Ie** were doubled, indicating the presence of two isomers (*E* and *Z*) at a ratio of 80 : 20 to 91 : 9 (calculated by the intensities of signals from the ester methyl protons). Presumably, the major isomer has *E* configuration.

Ethyl 3-benzylideneamino-3-phenylpropanoate (Ia). Yield 87%, transparent mobile liquid. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: major isomer: 1.07 t (3H, CH_3, ^3J = 7.3 Hz), 2.94–2.90 m (2H, CH_2), 3.99 m (2H, OCH_2), 4.82 d.d (1H, C**H**Ph, ^3J = 3.7, 7.8 Hz), 7.23–7.38 m (3H, H_{arom}), 7.48–7.41 m (5H, H_{arom}), 7.79–7.74 m (2H, H_{arom}), 8.45 s (1H, CH=N); minor isomer: 1.12 t (3H, CH_3, ^3J = 7.0 Hz); isomer ratio 83 : 17.

Ethyl 3-benzylideneamino-3-(4-bromophenyl)-propanoate (Ib). Yield 85%, light yellow mobile

liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: major isomer: 1.15 t (3H, CH_3, ^3J = 7.1 Hz), 2.84 d.d (1H, CH_2, ^2J = 15.5, ^3J = 4.9 Hz), 2.97 d.d (1H, CH_2, ^2J = 15.4, ^3J = 9.0 Hz), 4.06 q (2H, OCH_2, ^3J = 7.1 Hz), 4.81 d.d (1H, C**H**Ph, ^3J = 4.9, 9.0 Hz), 7.34 d (2H, H_{arom}, ^3J = 8.4 Hz), 7.37–7.43 m (3H, H_{arom}), 7.46 d (2H, H_{arom}, ^3J = 8.4 Hz), 7.76 d (2H, H_{arom}), 8.38 s (1H, CH=N); minor isomer: 1.23 t (3H, CH_3); isomer ratio 80:20.

Ethyl 3-(4-bromobenzylideneamino)-3-phenylpropanoate (Ic). Yield 82%, yellowish mobile liquid. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: major isomer: 1.06 t (3H, CH_3, ^3J = 7 Hz), 2.94–2.89 m (2H, CH_2), 3.98 m (2H, OCH_2), 4.82 d.d (1H, C**H**Ph, ^3J = 5.9 Hz), 7.30–7.23 m (1H, H_{arom}), 7.37–7.31 m (2H, H_{arom}), 7.45–7.41 m (2H, H_{arom}), 7.65 d (2H, H_{arom}, ^3J = 8.6 Hz), 7.71 d (2H, H_{arom}, ^3J = 8.6 Hz), 8.44 s (1H, CH=N); minor isomer: 1.12 t (3H, CH_3, ^3J = 7 Hz); isomer ratio 92:8. ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: major isomer: 14.5 (CH_3), 43.8 (CH_2), 60.6 (CH_2O), 71.7 (**C**HPh), 125.4 (CBr), 127.8 (2C, CH_{Ph}), 128.1 (CH_{Ph}), 129.3 (2C, CH_{Ph}), 130.7 (2C, CH_{Ar}), 132.5 (2C, CH_{Ar}), 136.4 (C_{Ar}), 143.8 (C_{Ph}), 160.9 (C=N), 171.1 (C=O). Found, %: C 59.81; H 4.98; N 3.97. $C_{18}H_{18}BrNO_2$. Calculated, %: C 60.01; H 5.04; N 3.89.

Ethyl 3-(3,4-dimethoxybenzylideneamino)-3-phenylpropanoate (Id). Yield 82%, transparent mobile liquid. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: major isomer: 1.07 t (3H, CH_3, ^3J = 7.0 Hz), 2.90 m (2H, CH_2), 3.78 s (3H, OCH_3), 3.79 s (3H, OCH_3), 3.99 q (2H, OCH_2, ^3J = 7 Hz), 4.77 t (1H, C**H**Ph, ^3J = 6.9 Hz), 7.01 d (1H, H_{arom}, ^3J = 8.3 Hz), 7.38–7.22 m (5H, Ph), 7.46–7.41 (2H, H_{arom}), 8.33 s (1H, CH=N); minor isomer: 1.12 t (3H, CH_3, ^3J = 7.3 Hz); isomer ratio 88:12. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 171.3 (C=O), 160.9 (C=N), 151.4, 149.2, 143, 129.4, 128.6, 127, 123.3, 110.4 (OCH_3), 109.1 (OCH_3), 70.9 (CH_{Ar}), 60.4 (OCH_2), 43.8 (CH_2), 14.2 (CH_3). Found, %: C 70.14; H 6.43; N 3.90. $C_{20}H_{23}NO_4$. Calculated, %: C 70.38; H 6.75; N 4.11.

Ethyl 3-(2,4-dichlorobenzylideneamino)-3-phenylpropanoate (Ie). Yield 75%, transparent mobile liquid. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: major isomer: 1.08 t (3H, CH_3, ^3J = 7.2 Hz), 2.94 m (2H, CH_2), 4.01 q (2H, OCH_2, ^3J = 7.3 Hz), 4.93 t (1H, C**H**Ph, ^3J = 6.5 Hz), 7.38–7.23 m (3H, H_{arom}), 7.39–7.34 m (3H, H_{arom}), 7.53–7.43 (3H, H_{arom}), 7.71 s (1H, H_{arom}), 7.98 d (1H, H_{arom}, ^3J = 8.3 Hz), 8.73 s (1H, CH=N); minor isomer: 1.12 t (3H, CH_3, ^3J = 6.9 Hz); isomer ratio 91:9. Found, %: C 61.46; H 4.68; N 3.88. $C_{18}H_{17}Cl_2NO_2$. Calculated, %: C 61.71; H 4.86; N 4.00.

3-Amino-3-phenylpropanoic acid (IIa). Yield 60%, white crystals, mp 219–220°C (decomp.); published data: mp 221–223°C (decomp.) [23], 235–237°C [38]. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.35–2.42 m (2H, CH_2), 4.14 t (1H, PhC**H**, ^3J = 7.3 Hz), 7.14–7.42 m (5H, H_{arom}).

3-Amino-3-(4-bromophenyl)propanoic acid (IIb). Yield 61%, white crystals, mp 232°C (decomp.); published data [37]: mp 234°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.41–2.52 m (2H, CH_2), 4.13 t (1H, PhC**H**, ^3J = 7.33 Hz), 7.19–7.45 m (4H, H_{arom}). Found, %: C 44.21; H 4.16; N 5.63. $C_9H_{10}BrNO_2$. Calculated, %: C 44.29; H 4.13; N 5.74.

Ethyl 3-amino-3-phenylpropanoate hydrochloride (IIIa). Yield 98%, colorless crystals, mp 140°C; published data: mp 138–141°C (decomp.) [38], 141–144°C [39]. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.16 t (3H, CH_3, ^3J = 7.1 Hz), 3.12 d.d (1H, CH_2, ^2J = 16.6, ^3J = 7.5 Hz), 3.21 d.d (1H, CH_2, ^2J = 16.6, ^3J = 7.2 Hz), 4.11 q (2H, OCH_2, ^3J = 7.1 Hz), 4.81 t (1H, PhC**H**, ^3J = 7.3 Hz), 7.44–7.58 m (5H, H_{arom}).

Ethyl 3-amino-3-(4-bromophenyl)propanoate hydrochloride (IIIb). Yield 97%, colorless crystals. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.13 t (3H, CH_3, ^3J = 7.3 Hz), 3.05–3.20 m (2H, CH_2), 4.10 q (2H, OCH_2), 4.77 t (1H, CH, ^3J = 7.4 Hz), 7.34–7.65 m (4H, H_{arom}).

The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-400 spectrometer at 400 and 100 MHz, respectively; the chemical shifts were determined relative to the residual proton and carbon signals of the deuterated solvent.

This study was performed under financial support by the Ministry of Education and Science of the Russian Federation (state contract no. 16.512.11.2240).

REFERENCES

1. Mahmood-Ul-Hassan, Chohan, Z.H., Scozzafava, A., and Supuran, C.T., *J. Enzyme Inhib. Med. Chem*., 2004, vol. 19, p. 263; Puccetti, L., Fasolis, G., Vullo, D., Chohan, Z.H., Scozzafava, A., and Supuran, C.T., *Bioorg. Med. Chem. Lett*., 2005, vol. 15, p. 3096.
2. Hewett-Emmett, D., *The Carbonic Anhydrases: New Horizons*, Chegwidden, W.R., Carter, N.D., and Edwards, Y.H., Eds., Basel: Birkhäuser, 2000, p. 29; Supuran, C.T. and Scozzafava, A., *Expert Opin. Ther. Pat*., 2000, vol. 10, p. 575.

3. Renard, J.P., Giraud, J.M., and Oubaaz, A., *J. Fr. Ophthalmol*., 2004, vol. 27, p. 701.
4. Supuran, C.T., *Expert Opin. Ther. Pat*., 2003, vol. 13, p. 1545.
5. Supuran, C.T., Vullo, D., Manole, G., Casini, A., and Scozzafava, A., *Curr. Med. Chem. Cardiovasc. Hematol. Agents*, 2004, vol. 2, p. 49.
6. Robertson, N., Potter, C., and Harris, A.L., *Cancer Res*., 2004, vol. 64, p. 6160.
7. Epstein, D.L. and Grant, W.M., *Arch. Ophthalmol*., 1977, vol. 95, no. 8, p. 1378.
8. Nasr, G., Petit, E., Supuran, C.T., Winum, J.-Y., and Barboiu, M., *Bioorg. Med. Chem. Lett*., 2009, vol. 19, p. 6014.
9. El-Masry, A.N., Fahmy, H.H., and Abdelwahed, S.H.A., *Molecules*, 2000, vol. 21, p. 1429.
10. Baseer, M.A., Jadhav, V.D., Phule, R.M., Archana, Y.V., and Vibhute, Y.B., *Orient. J. Chem*., 2000, vol. 16, no. 3, p. 553.
11. Hfndeya, S.N., Sriram, D., Nath, G., and De Clercq, E., *Il Farmaco*, 1999, vol. 54, p. 624.
12. Singh, W.M. and Dash, B.C., *Pesticides*, 1988, vol. 22, no. 11, p. 33.
13. Samadhiya, S. and Halve, A., *Orient. J. Chem*., 2001, vol. 17, no. 1, p. 119.
14. Desai, S.B., Desai, P.B., and Desai, K.R., *Heterocycl. Commun*., 2001, vol. 7, no. 1, p. 83.
15. Hodnett, E.M. and Dunn, W.J., *J. Med. Chem*., 1970, vol. 13, no. 4, p. 768.
16. Staudinger, H., *Ber*., 1907, vol. 40, p. 1145; Staudinger, H., *Justus Liebigs Ann. Chem*., 1907, vol. 356, p. 51.
17. Liu, Z.-Y., Wang, Y.-M., Li, Z.-R., Jiang, J.-D., and Boykin, D.W., *Bioorg. Med. Chem. Lett*., 2009, vol. 19, p. 5661.
18. Todorov, A.R., Kurteva, V.B., Bontchev, R.P., and Vassilev, N.G., *Tetrahedron*, 2009, vol. 65, p. 10339.
19. Bhalla, A., Venugopalan, P., and Bari, S.S., *Tetrahedron*, 2006, vol. 62, p. 8291; Fu, N. and Tidwell, T.T., *Tetrahedron*, 2008, vol. 64, p. 10465; Cheemala, M.N. and Knochel, P., *Org. Lett*., 2007, vol. 9, p. 3089; Bari, S.S., Reshma, Bhalla, A., and Hundal, G., *Tetrahedron*, 2009, vol. 65, p. 10060; Hu, L., Wang, Y., Li, B., Du, D.-M., and Xu, J., *Tetrahedron*, 2007, vol. 63, p. 9387.
20. Shang, G., Yang, Q., and Zhang, X., *Angew. Chem., Int. Ed*., 2006, vol. 45, p. 6360; Ross, N.A., MacGregor, R.R., and Bartsch, R.A., *Tetrahedron*, 2004, vol. 60, p. 2035; Joffe, A.L., Thomas, T.M., and Adrian, J.C., Jr., *Tetrahedron Lett*., 2004, vol. 45, p. 5087; Veverkova, E., Strasserova, J., Sebesta, R., and Toma, S., *Tetrahedron: Asymmetry*, 2010, vol. 21, p. 58; Zhang, H., Syed, S., and Barbas, C.F. III, *Org. Lett*., 2010, vol. 12, p. 708.
21. Soengas, R.G., Segad, J., Jimenez, C., and Rodriguez, J., *Tetrahedron*, 2011, vol. 67, p. 2617.
22. Choudhury, L.H. and Parvin, T., *Tetrahedron*, 2011, vol. 67, p. 8213.
23. Soloshonok, V.A., Fokina, N.A., Rybakova, A.V., Shishkina, I.P., Galushko, S.V., Sorochinsky, A.E., Kukhar, V.P., Savchenko, M.V., and Švedas, V.K., *Tetrahedron: Asymmetry*, 1995, vol. 6, p. 1601.
24. Soloshonok, V.A., Švedas, V.K., Kukhar, V.P., Kirilenko, A.G., Galaev, I.Yu., Kozlova, E.V., Shishkina, I.P., and Galushko, S.V., *Synlett*, 1993, p. 339; Romanova, N.N., Gravis, A.G., Kudan, P.V., and Bundel', Ju.G., *Mendeleev Commun*., 2001, no. 1, p. 26; Romanova, N.N., Gravis, A.G., Kudan, P.V., Leshcheva, I.F., and Zyk, N.V., *Russ. J. Org. Chem*., 2003, vol. 39, p. 692; Romanova, N.N., Tallo, T.G., Rybalko, I.I., Zyk, N.V., and Shvyadas, V.K., *Chem. Heterocycl. Compd*., 2011, no. 4, p. 395.
25. Adriaenssens, L.V. and Hartley, R.C., *J. Org. Chem*., 2007, vol. 72, p. 10287.
26. Mokhallalati, M.K. and Pridgen, L.N., *Synth. Commun*., 1993, vol. 23, no. 14, p. 2055.
27. Schiff, H., *Justus Liebigs Ann. Chem*., 1864, vol. 131, p. 118.
28. Taguchi, K. and Westheimer, F.H., *J. Org. Chem*., 1971, vol. 36, p. 1570.
29. Hania, M.M., *E-J. Chem*., 2009, vol. 6, no. 3, p. 629. doi 10.1155/2009/104058
30. Guzen, K.P., Guarezemini, A.S., Orfao, A.T.G., Cella, R., Pereira, C.M.P., and Stefani, H.A., *Tetrahedron Lett*., 2007, vol. 48, p. 1845.
31. Caddick, S.R., *Tetrahedron*, 1995, vol. 51, p. 10403; Lidstrom, P., Tierney, J., Wathey, B., and Westman, J., *Tetrahedron*, 2001, vol. 57, p. 9225; Romanova, N.N., Gravis, A.G., and Zyk, N.V., *Usp. Khim*., 2005, vol. 74, p. 1059; Caddick, S. and Fitzmaurice, R., *Tetrahedron*, 2009, vol. 65, p. 3325.
32. Varma, R.S., Dahiya, R., and Kumar, S., *Tetrahedron Lett*., 1997, vol. 38, p. 2039.
33. Godoy-Alcantar, C., Yatsimirsky, A.K., and Lehn, J.-M., *J. Phys. Org. Chem*., 2005, vol. 18, p. 979.
34. Simon, A., Simon, C., Kanda, T., Nagashima, S., Mitoma, Y., Yamada, T., Mimura, K., and Tashiro, M., *J. Chem. Soc., Perkin. Trans. 1*, 2001, p. 2071.
35. Saggiomo, V. and Luning, U., *Tetrahedron Lett*., 2009, vol. 50, p. 4663.
36. Rodionow, W.M. and Postovskaja, E.A., *J. Am. Chem. Soc*., 1929, vol. 51, p. 841; Rodionow, W.M., *J. Am. Chem. Soc*., 1929, vol. 51, p. 847.
37. Tan, C.Y.K. and Weaver, D.F., *Tetrahedron*, 2002, vol. 58, p. 7449.
38. Nejman, M., Sliwinska, A., and Zwierzak, A., *Tetrahedron*, 2005, vol. 61, p. 853.
39. Tasnadi, G., Forro, E., and Fulop, F., *Tetrahedron: Asymmetry*, 2008, vol. 19, p. 2072.