ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 3, pp. 447–451. © Pleiades Publishing, Ltd., 2008.
Published in Russian in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 3, pp. 449–453.

Facile and Efficient Synthesis of 1-[2-(6,7-Dimethyl-3,4-dihydronaphthalen-2-yl)ethyl]pyrrolidine Hydrochloride*

Jiann-Jyh Huang[a], Mou-Yung Yeh[b,c], and Fung Fuh Wong[d]

[a] *Development Center for Biotechnology, No. 101, Lane 169, Kangning St.. Xizhi City, Taipei County, Taiwan 221, China*

[b] *Department of Chemistry, National Cheng Kung University, No. 1, Ta Hsueh Rd., Tainan, Taiwan 70101, China*

[c] *Nan Jeon Institute of Technology, No. 178, Chaocin Rd., Yanshuei Township, Tainan County 737, Taiwan, China*

[d] *Environmental Resource Management Research Center, National Cheng Kung University, No. 500, Sec. 3, An-ming Rd., Tainan City, Taiwan 709, China*
e-mail: wongfungfuh@yahoo.com.tw

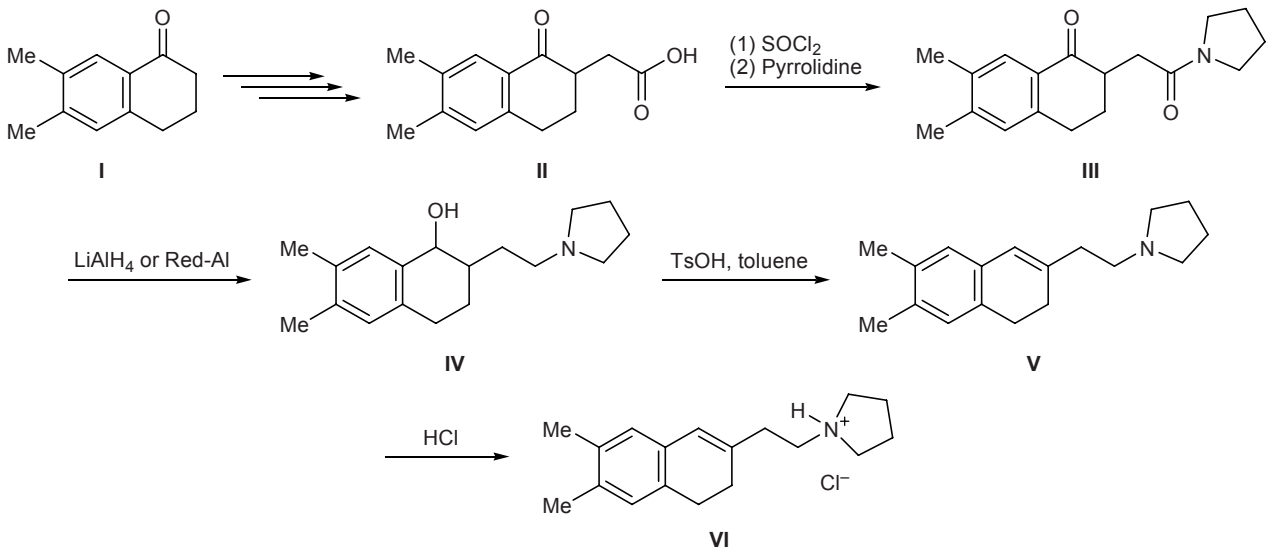
Received November 1, 2005

Abstract—An efficient and facile procedure for the preparation of 1-[2-(6,7-dimethyl-3,4-dihydronaphthalen-2-yl)ethyl]pyrrolidine hydrochloride from 6,7-dimethyl-1,2,3,4-tetrahydronaphtalen-1-one in four steps is proposed. It includes one-step synthesis of 1-(6,7-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid as key intermediate and subsequent transformations of functional groups therein.

DOI: 10.1134/S1070428008030214

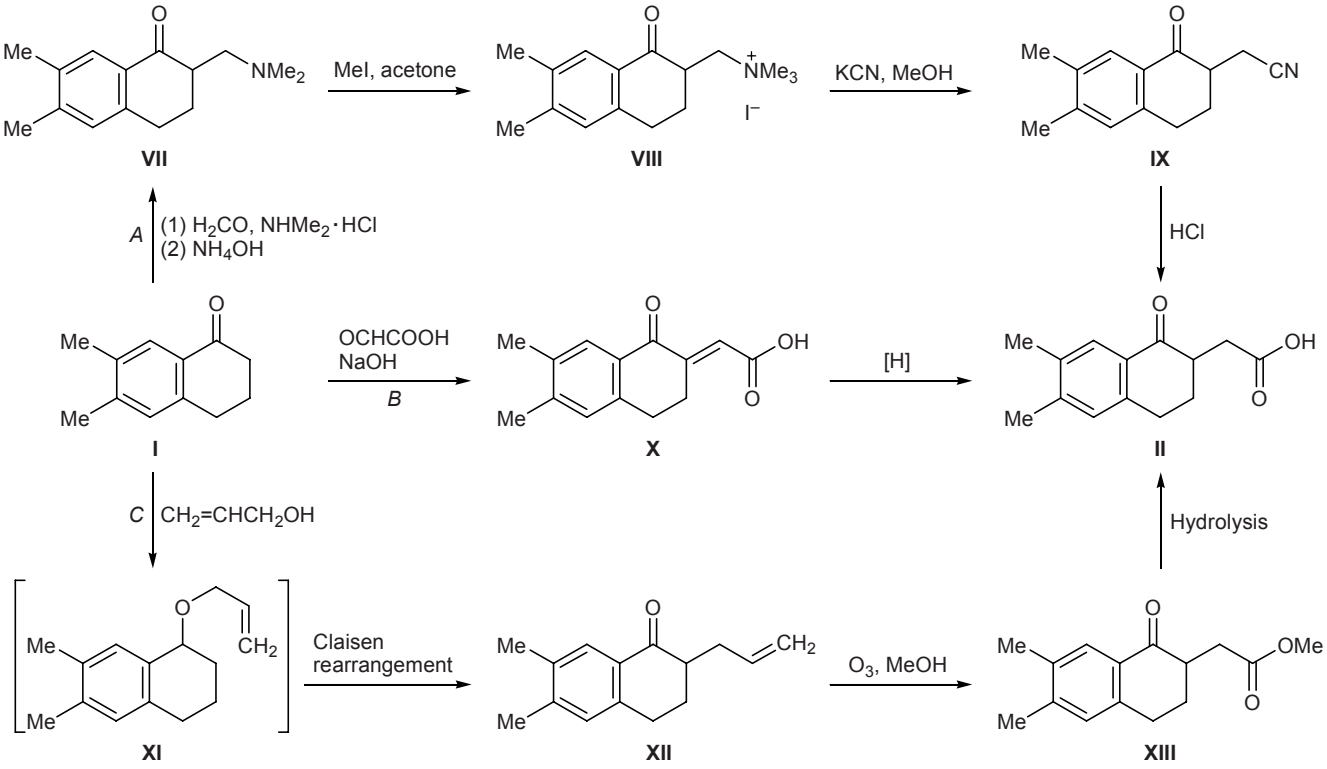
1-[2-(6,7-Dimethyl-3,4-dihydronaphthalen-2-yl)-ethyl]pyrrolidine hydrochloride (**VI**) is an analgesic, tranquilizing agent for mammals, and remedy for frequent urination and urinary incontinence [1–3]. Traditional methods for the preparation of compound **VI** involve the use of 6,7-dimethyl-1,2,3,4-tetrahydronaphtalen-1-one (**I**) as starting material to generate the key γ-keto carboxylic acid **II**, followed by amidation (**II**→**III**), reduction (**III**→**IV**), dehydration (**IV**→**V**), and salt formation (**V**→**VI**) [4] (Scheme 1). These methods include tedious steps for the preparation of compound **II** and isolation of unnecessary intermediate **V**. Furthermore, the yield of the target product cannot be regarded as satisfactory, and the procedures are not suitable for the development of large-scale processes. Three representative methods were reported for the

Scheme 1.



* The text was submitted by the authors in English.

Scheme 2.

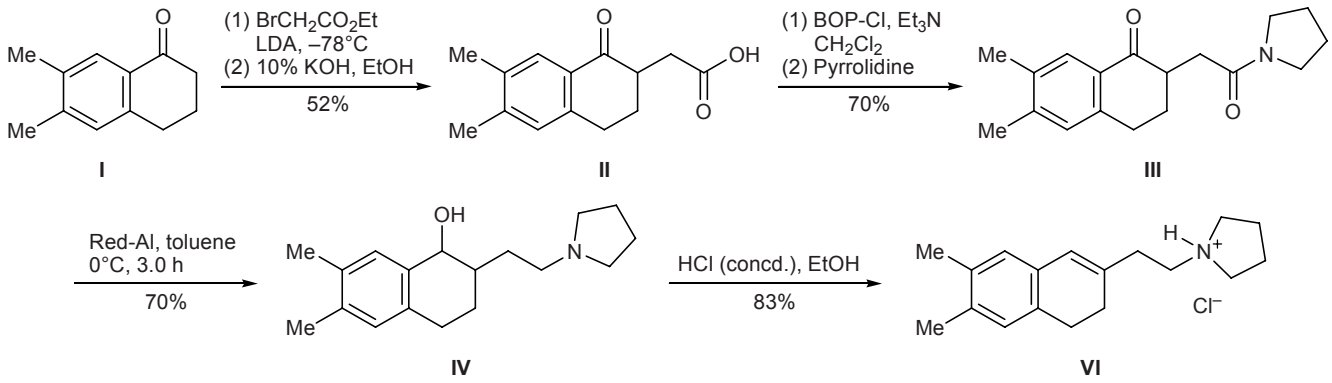


synthesis of compound **II** from 6,7-dimethyl-1,2,3,4-tetrahydronaphtalen-1-one (**I**) (Scheme 2). Method *A* is based on the reaction of compound **I** with a Mannich base as the key step to afford amine **VII**. Methylation of the amino group in **VII** [5] gives quaternary salt **VIII** which is then treated with potassium cyanide to replace the trimethylammonio group by cyano. Hydrolysis of the cyano group in nitrile **IX** leads to desired acid **II** [6]. This synthetic route requires four steps, and the yield is low. Method *B* includes aldol condensation of compound **I** with glyoxylic acid to generate compound **X** [7], which is subjected to catalytic hydrogenation to afford acid **II** [8]. Though this synthetic strategy requires less steps than does method *A*, the yield in the first step (**I** → **X**) is poor (30%). Method *C* involves the Claisen rearrangement of allyl vinyl ether **XI** to obtain ketone **XII**, followed by ozonolysis to generate the corresponding γ-keto carboxylate **XIII** [9]. Hydrolysis of **XIII** provides key intermediate **II**. The overall yield of **II** according to method *C* is also poor.

To improve the procedure for the preparation of compound **VI**, we have developed a new synthetic pathway where key intermediate **II** is obtained via one-pot reaction (Scheme 3). Initially, 1,2,3,4-tetrahydronaphtalen-1-one (**I**) was treated with ethyl bromoacetate [10] in the presence of lithium diisopropylamide at –78°C. The subsequent hydrolysis of the crude reaction mixture containing ethyl ester intermediate (see Experimental) with potassium hydroxide in ethanol gave the corresponding carboxylic acid **II** in an overall yield of 52%. This procedure includes two transformations, and the yield is better than in the traditional methods described above.

For the synthesis of amide **III**, the carboxylic acid group in **II** was first activated with the use of *N*,*N*′-bis-[2-oxo-1,3-oxazolidin-3-yl]phosphorodiamidic chloride (BOP-Cl) [11] under microwave irradiation, and pyrrolidine was then added to the reaction mixture. We thus isolated compound **III** in 70% yield. The reduction of the ketone and amide carbonyl groups in **III** was effected using sodium bis(2-methoxyethoxy)hydridoaluminate (Red-Al) as reducing agent, taking into account its good solubility in aromatic hydrocarbons, stability in air, and reducing potency [12]. In such a way we succeeded in obtaining compound **IV** in 70% yield. The last step was simultaneous dehydration and salt formation, which were achieved using ethanolic hydrochloric acid. Compound **VI** was thus isolated in 83% yield. Unlike the traditional procedure involving *p*-tolenesulfonic acid as dehydrating agent, the use of hydrogen chloride is more advantageous due to

Scheme 3.



low cost and no need of isolating intermediate amine **V** (Scheme 1). The new synthetic procedure proposed by us consists of only four steps, and the overall yield is 21%, i.e., it is more efficient than the traditional methods. Moreover, the proposed procedure is suitable for enlarged syntheses.

EXPERIMENTAL

Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254, Merck). Column chromatography was carried out using silica gel 60 (0.063-0.200 mm, Merck). The IR spectra were measured on a Bomem Michelson Series FT-IR spectrometer; the wavenumbers were referenced to polystyrene absorption (1601 cm^{-1}). The ^1H and ^{13}C NMR spectra were obtained on Varian Unity-300 and Bruker spectrometers at 300 and 75 MHz, respectively, using $CDCl_3$ and DMSO-d_6 as solvents; the ^{13}C chemical shifts were measured relative to the solvent signal ($CDCl_3$, δ_C 77.0 ppm). The elemental compositions were determined on a Heraeus CHN-O RAPID analyzer. The purity of all products was >99% (according to the HPLC data).

1-(6,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (II) [1]**.** A 2.5-M solution of *n*-butyllithium in hexane, 35.0 ml (55.6 mmol, 1.2 equiv), was added to a solution of 5.33 g (50.9 mmol, 1.1 equiv) of diisopropylamine in tetrahydrofuran. The mixture was stirred for 30 min at –20 to –10°C, cooled to –78°C, and stirred for an additional 1.0 h. A solution of 8.50 g (46.3 mmol, 1.0 equiv) of 5,6-dimethyl-1,2,3,4-tetrahydronaphthalen-1-one (**I**) in 10 ml of anhydrous THF was added dropwise over a period of 10 min, the mixture was stirred for 30 min at –78°C, and 7.73 g (46.3 mmol, 1.0 equiv) of ethyl bromoacetate was added dropwise to the resulting solution. The mixture was allowed to warm up to room temperature and concentrated to remove THF. The residue was diluted with 250 ml of ethyl acetate, washed with 5% aqueous $NaHCO_3$ (2×50 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in 100 ml of 10% ethanolic KOH, the solution was heated for 3 h under reflux, cooled to room temperature, and washed with methylene chloride (2×50 ml). The aqueous phase was acidified with concentrated hydrochloric acid, and the precipitate was filtered off, washed with hexane (2×20 ml), and recrystallized from hexane. Yield 5.63 g (24.1 mmol, 52%), light yellow solid. ^1H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 1.64–1.89 m (1H), 2.09–2.11 m (1H), 2.21 s (3H, CH_3), 2.24 s (3H, CH_3), 2.35–2.49 m (1H), 2.66–3.02 m (5H), 7.09 s (1H, H_{arom}), 7.60 s (1H, H_{arom}), 12.18 br.s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$–DMSO-d_6), δ_C, ppm: 19.62, 19.99, 20.07, 36.28, 109.74, 121.69, 123.03, 126.96, 129.34, 132.56, 134.66, 136.72, 146.65, 175.91. IR spectrum (neat), ν, cm^{-1}: 3452 br (OH), 2930 m, 1801 s (C=O), 1648 m, 1384 m, 1115 m, 1035 m, 864 m. Mass spectrum, *m*/*z* (I_{rel}, %): 234 $[M]^+$ (2), 216 (5), 204 (3), 188 (5), 176 (15), 162 (12), 133 (18), 119 (18), 84 (30), 66 (47), 46 (100), 30 (10), 18 (71), 16 (18). The intermediate ethyl ester was isolated and its structure was identified: ^1H NMR spectrum: ($CDCl_3$), δ, ppm: 1.25 t (3H, CH_3, J = 5.4 Hz), 1.67–1.91 m (1H), 2.19–2.36 m (1H), 2.23 s (3H, CH_3), 2.25 s (3H, CH_3), 2.37–2.48 m (1H), 2.67–3.09 m (4H), 4.15 q (2H, CH_2, J = 5.4 Hz), 6.98 s (1H, H_{arom}), 7.75 s (1H, H_{arom}); ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.19, 19.32, 19.90, 28.69, 29.45, 35.16, 44.67, 60.46, 128.07, 129.20, 130.00, 135.16, 141.62, 143.12, 177.65, 199.31.

2-[2-Oxo-2-(pyrrolidin-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-1-one (III) [1]**.** A solution of 5.67 g (25.5 mmol, 1.0 equiv) of compound **II** in 50 ml of

methylene chloride was cooled to 0°C under nitrogen using an ice bath. *N*,*N*′-Bis(2-oxo-1,3-oxazolidin-3-yl]-phosphorodiamidic chloride, 6.49 g (25.5 mmol, 1.0 equiv), and triethylamine, 7.0 ml (51.0 mmol, 2.0 equiv), were added to the solution, the mixture was stirred for 1.0 h, and pyrrolidine, 2.20 ml (25.5 mmol, 1.0 equiv), was added dropwise over a period of 1.0 h. When the reaction was complete, the mixture was diluted with 150 ml of methylene chloride, washed with an aqueous solution of $NaHCO_3$ (2×30 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using 5% of MeOH in CH_2Cl_2 as eluent to isolate 5.08 g (17.8 mmol, 70%) of compound **III** as a yellow solid, R_f 0.50 (5% of MeOH in CH_2Cl_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.76–1.93 m (5H), 2.18 s (3H, CH_3), 2.19 s (3H, CH_3), 2.18–2.60 m (2H), 2.76–2.81 m (2H), 2.96–3.11 m (4H), 3.12–3.54 m (4H), 6.92 s (1H, H_{arom}), 7.69 s (1H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.07, 19.80. 24.22, 25.89, 28.67, 29.84, 34.90, 44.57, 45.50, 46.40, 127.75, 129.54, 130.07, 134.71, 141.65, 142.71, 159.93, 199.28. IR spectrum (neat), ν, cm^{-1}: 3488 br, 2948 m (C–H_{arom}), 1638 m (C=O), 1612 m, 1442 m, 1255 m, 1181 m, 918 m. Mass spectrum, *m*/*z* (I_{rel}, %): 285 $[M]^+$ (3), 278 (2), 221 (93), 189 (3), 170 (11), 149 (21), 135 (21), 122 (100), 105 (37), 103 (26), 91 (21), 77 (22), 58 (18), 41 (21), 30 (47), 18 (34).

2-[2-(Pyrrolidin-1-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-1-ol (IV) [1]**.** A solution of 1.71 g (6.00 mmol, 1.0 equiv) of compound **III** in 50 ml of toluene was cooled to 0°C under nitrogen using an ice bath, and a 3.5-M solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene (13.0 ml, 18.0 mmol, 3.0 equiv) was added dropwise. When the reaction was complete, the mixture was quenched with 10 ml of cold methanol in an ice bath. The resulting solution was concentrated, diluted with 200 ml of ethyl acetate, washed with aqueous potassium sodium (+)-tartrate tetrahydrate (2×20 ml) and a solution of sodium chloride (2×20 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride as eluent to isolate 1.15 g (4.20 mmol, 70%) of compound **IV** as a light yellow solid, R_f 0.25 (10% of MeOH in CH_2Cl_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.60–1.71 m (5H), 1.73–1.86 m (4H), 2.16 s (3H, CH_3), 2.22 s (3H, CH_3), 2.49–2.55 m (3H), 2.68–2.80 m (5H), 4.37 d (1H, 1-H, J = 6.8 Hz), 6.80 s (1H, H_{arom}), 7.42 s (1H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 19.13, 23.27, 28.97, 30.02, 35.66, 44.41, 53.38, 55.37, 73.58, 128.20, 128.87, 133.10, 133.91, 134.29, 137.10. IR spectrum (neat), ν, cm^{-1}: 3480 br (OH), 2922 w (=C–H), 2803 s, 1500 m, 1452 s, 1383 m, 1288 m, 1135 m, 1091 m, 878 m, 753 m, 663 m.

1-[2-(6,7-Dimethyl-3,4-dihydronaphthalen-2-yl)-ethyl]pyrrolidine hydrochloride (VI) [1]**.** Compound **IV**, 3.30 g (12.1 mmol), was added to 30 ml of a solution of HCl in ethanol, and the mixture was stirred for 5–8 h under reflux. It was then concentrated under reduced pressure, and the residue was recrystallized from methylene chloride–hexane. Yield 2.93 g (83%), white solid, mp 209–212°C (from CH_2Cl_2–hexane). ^{1}H NMR spectrum ($CDCl_3$–DMSO-d_6), δ, ppm: 1.87–2.06 m (4H), 2.13–2.18 m (2H), 2.14 s (6H, CH_3), 2.50–2.70 m (4H, CH_2CH_2), 2.80–2.92 m (2H, NCH_2), 3.10–3.25 m (2H, NCH_2), 3.55–3.78 m (2H, NCH_2), 5.16 s (1H, 1-H), 6.67 s and 6.76 s (1H each, 5-H, 8-H), 12.06 br.s (1H, NH^+); ^{13}C NMR spectrum ($CDCl_3$–DMSO-d_6), δ_C, ppm: 19.02, 19.20, 23.13, 27.15, 32.97, 53.46, 124.55, 125.93, 128.48, 131.12, 131.31, 133.99, 134.13, 134.86. IR spectrum (reflect diffuse), ν, cm^{-1}: 3501 br (NH), 2930 s, 2664 s, 2578 s, 2477 s, 1455 m, 1364 m, 1222 m, 1073 m, 1023 m, 901 m, 886 m, 503 m. Mass spectrum, *m*/*z* (I_{rel}, %): 255 $[M]^+$ (4), 185 (3), 171 (14), 155 (18), 141 (19), 128 (10), 115 (8), 84 (100), 55 (11), 42 (18). Found, %: C 74.04; H 9.02; N 4.86. $C_{18}H_{26}ClN$. Calculated, %: C 74.07; H 8.98; N 4.80.

The authors thank the Ministry of Education of Republic of China and the National Science Council of Republic of China for financial support.

REFERENCES

1. Kai, N., Kanehira, A., Morie, T., Hino, K., Kawashima, K., Shimizu, I., and Akiyama, K., PCT/JP Patent Appl. no. 1996-001009, 1996; WO Patent Appl. Publ. no. 1996-033169).
2. Willard, M.W., US Patent no. 4022791, 1977.
3. Welch, W.M., Harbert, C.A., Sarges, R., Stratten, W.P., and Weissman, A., *J. Med. Chem*., 1977, vol. 20, p. 699; Welch, W.M., Plattner, J.J., Stratten, W.P., and Harbert, C.A., *J. Med. Chem*., 1978, vol. 21, p. 257.
4. Orgueira, H.A., Fokas, D., Isome, Y., Chan, P.C.-M., and Baldino, C.M., *Tetrahedron Lett*., 2005, vol. 46, p. 2911.
5. March, J., *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, New York: Wiley, 1991, 4th ed., p. 399.

6. Wilgus, C.P., Downing, S., Molitor, E., Bains, S., Pagni, R.M., and Kabalka, G.W., *Tetrahedron Lett*., 1995, vol. 36, p. 3469.
7. Newman, M.S., Sagar, W.C., and Cochrane, C.C., *J. Org. Chem*., 1958, vol. 23, p. 1832.
8. Chen, J.-X., Daeuble, J.F., and Stryker, J.M., *Tetrahedron*, 2000, vol. 56, p. 2789.
9. Wu, E.S.C. and Kover, A., *Synth. Commun*., 1994, vol. 24, p. 273; Hailes, H.C., Isaac, B., and Javaid, M.H., *Tetrahedron Lett*., 2001, vol. 42, p. 7325.
10. Hatch, L.F., Alexander, H.E., and Randolph, J.D., *J. Org. Chem*, 1950, vol. 14, p. 654.
11. Cabré-Castellvi, J. and Palomo-Coll, A.L., *Tetrahedron Lett*., 1980, vol. 21, no. 43, p. 4179.
12. Bažant, V., Čapka, M., Černý, M., Chvalovský, V., Kochloefl, K., Kraus, K., and Málek, J., *Tetrahedron Lett*., 1968, vol. 9, no. 29, p. 3303; Černý, M. and Málek, J., *Tetrahedron Lett*., 1969, vol. 10, no. 22, p. 1739.