ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 7, pp. 1077–1081. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © A.A. Avetisyan, G.G. Tokmadzhyan, R.A. Piridzhanyan, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 7, pp. 1086–1090.

Synthesis of Heterospirans Containing a γ-Lactone Ring

A. A. Avetisyan, G. G. Tokmadzhyan, and R. A. Piridzhanyan

Yerevan State University, Yerevan, 375025 Armenia
e-mail: tokmajyang@yahoo.com

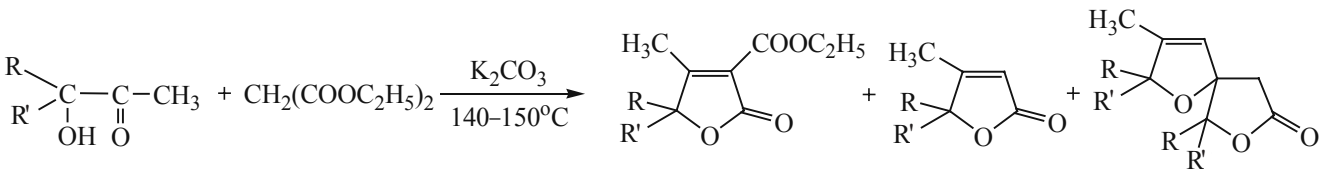
Received July 30, 2007

Abstract—Reactions of α-ketols with diethyl malonate at the molar ratio 2:1 in the presence of K_2CO_3 were investigated. The heterospiranes obtained contained a dihydrofuran and a γ-lactone rings. The optimum conditions for the synthesis of heterospiranes were found by varying the ratio of the initial compounds: α-ketoalcohol (or 2-ethoxycarbonyl-, 2-methoxycarbonyl-, 2-cyano-3,4,4-trimethyl-2-buten-4-olides), diethyl malonate, K_2CO_3, by varying the environment, and also the temperature and the time of the reaction.

DOI: 10.1134/S1070428008070221

One of the most general preparation methods of functionally substituted 2-buten-4-olides [furan-2(5*H*)-ones] consists in the condensation of α-ketoalcohols with compounds containing active methylene groups in the presence of basic reagents [1]. In the course of the search of optimum conditions for the preparation of 2-ethoxycarbonyl-3,4,4-trimethyl-2-buten-4-olide [ethyl 4,5,5-trimethyl-2-oxo-2,5-dihydro-furan-3-carboxylate (**I**)] from dimethylacetylcarbinol and diethyl malonate [2] in the presence of potassium carbonate we found that the heating of the initial reagents at the molar ratio 2:1 at 140–150°C led to the formation of three reaction products, among which one was the target lactone **I** (yield 15%), and another was 4,5,5-trimethylfuran-2(5*H*)-one (**II**) (yield 20%). The study of the structure of the third compound (yield 45%) by means of IR, ^{1}H NMR spectroscopy and mass spectrometry permitted its identification as 2,2,3,6,6-pentamethyl-1,7-dioxaspiro[4.4]non-3-en-8-one (**III**) [3].

The attempt to synthesize ethyl-4-methyl-2-oxo-1-oxaspiro[4.5]dec-3-ene-3-carboxylate (**V**) from 1-acetylcyclohexanol and diethyl malonate in the presence of potassium carbonate also gave a similar result. The major reaction product alongside previously known 4-methyl-1-oxaspiro[4.5]dec-3-en-2-one (**VI**) (yield 24%) and compound **V** (yield 12%) was 19-methyl-7,15-dioxatrispiro[5.1.0.5.3.2]nonadec-18-en-16-one (**VII**) (yield 35%) [3]. In order to define the limits of this fairly interesting reaction we introduced into the reaction with diethyl malonate the methylphenylacetylcarbinol. The reaction was carried out in the previously found optimum conditions: the molar ratio of diethyl malonate to the methylphenylacetylcarbinol 2:1, temperature 140°C, reaction time 10 h. Thus we obtained 4,5-dimethyl-5-phenylfuran-2(5*H*)-one (**VIII**) (33%), ethyl 4,5-dimethyl-2-oxo-5-phenyl-2,5-dihydrofuran-3-carboxylate (**IX**) (6%), and 2,3,6-trimethyl-2,6-diphenyl-1,7-dioxaspiro-[4.4]non-3-en-8-one (**X**) (30%). Therefore a method was



I, V, IX **II, VI, VIII** **III, VII, X**

I–III, R = R' = CH_3; **V–VII**, R, R' = $(CH_2)_5$; **VIII–X**, R = CH_3, R' = C_6H_5.

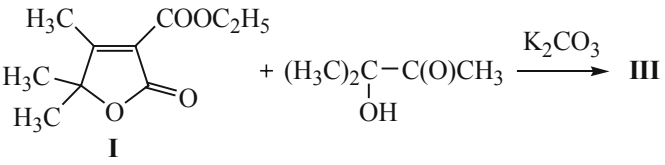
found for preparation of heterospiranes containing a γ-lactone and a dihydrofuran rings.

Natural and synthetic derivatives of γ-lactones, among them also spiro compounds containing the γ-lactone rings, are endowed with a wide range of biological action [4–7], many of them are used in the medical practice, and we believe that the more detailed investigation of the pathway of the found closure of the dihydrofuran ring and also of various factors affecting the yield of heterospiranes possessing the γ-lactone ring would be rational.

The condensation of α-ketoalcohol with diethyl malonate under the conditions of the phase-transfer catalysis (in the presence of potassium carbonate) provided not only 4,5-substituted ethyl 2-oxo-2,5-dihydrofuran-3-carboxylates **I, V**, and **IX**, but also to the products of their further condensation and transformation under the reaction conditions.

Apparently the key stage in the synthesis of spiro compounds **III, VII**, and **X** is the nucleophilic attack of a lactone allyl carbanion generated by the base on the carbonyl group of the ketoalcohol to form intermediate compounds **A**. The water elimination and the nucleophilic attack of a hydroxy group on the electron-deficient β-carbon atom by the type of Michael reaction results in spiro compounds **B** (Scheme 1). Their further hydrolysis under the reaction conditions and the decarboxylation leads to the formation of compounds **III**, **VII**, and **X**. The assumed reaction pathway [the primary formation of ethyl 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**I**), its condensation with dimethylacetylcarbinol, intramolecular addition to the activated double bond, hydrolysis of the ester group, and the decarboxylation] was tested on a sequence of reactions.

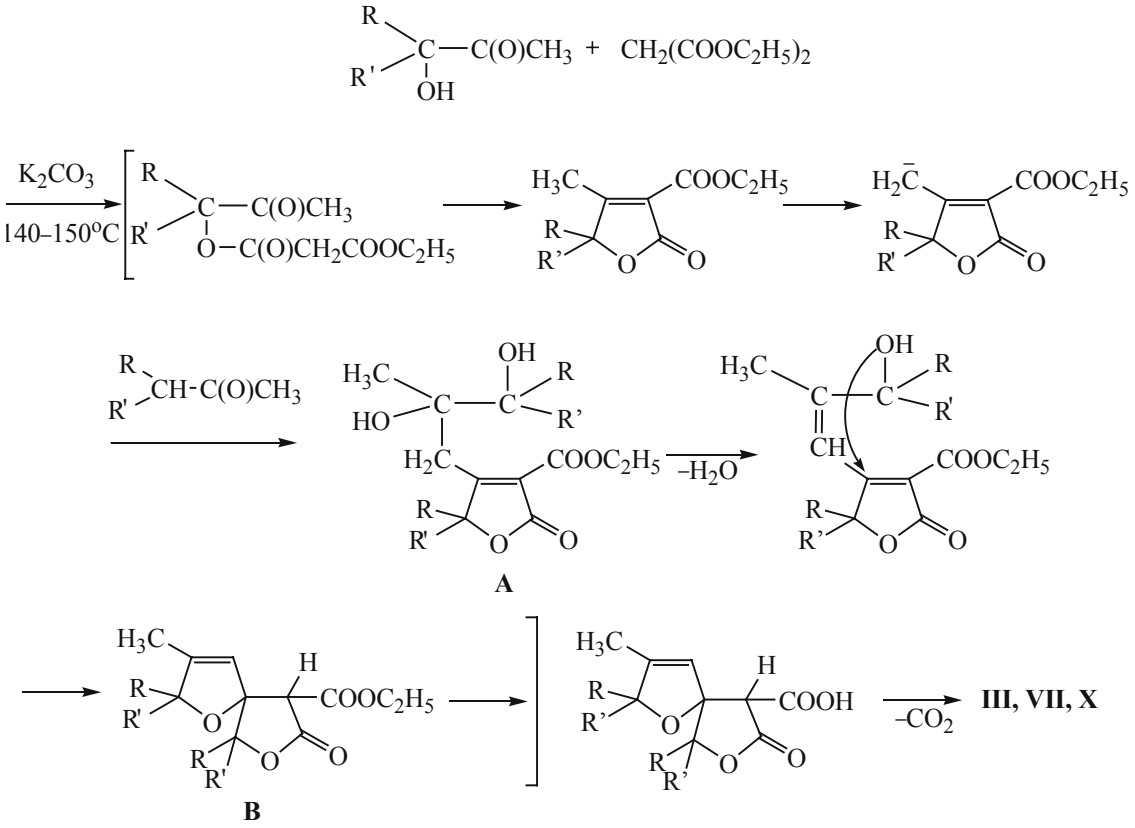
The reaction of compound **I** with dimethylacetylcarbinol under similar conditions resulted as expected in the formation of the corresponding heterospirane **III** in up to 63% yield depending on the reaction temperature.



I

However the reaction of 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid with dimethylacetyl-

Scheme 1.



carbinol gave spiro compound **III** only in 2% yield, and the reaction of compound **II** with dimethylacetylcarbinol did not go at all.

The active role in the reaction under study of the electron-acceptor fragment [$CH_3CH{=}C(COOC_2H_5)COO$] was proved by involving into the reaction with dimethylacetylcarbinol the diethyl ethylidenemalonate [8].

The closure of the dihydrofuran ring with the formation of compound **XI** proves the validity of our concept of the chemistry of this process (Scheme 2).

The effect of various factors on the yield of compound **III** we studied by an example of the reaction either of diethyl malonate or compound **I** with dimethylacetylcarbinol in the presence of K_2CO_3 (without solvent or in dimethyl sulfoxide).

The first set of experiments with the variation of reagents ratio and also of reaction temperature and duration showed that the yield of target compound **III** depended both on the molar reagents ratio and on the reaction temperature. The optimum reaction conditions giving compound **III** in 45% yield were as follows: molar ratio diethyl malonate–dimethylacetylcarbinol–K_2CO_3 1:0.5:1, temperature 140–150°C, reaction time 10 h. The reaction carried out in DMSO gave compound **III** only in 30% yield. In the latter case the main reaction product was compound **II**.

The second set of experiments included the reaction of compound **I** in the presence of K_2CO_3 at heating the reaction mixture in various manners for 7–8 h both without solvent and in DMSO. The best yield of compound **III** (63%) was obtained at the molar ratio lactone–ketoalcohol–K_2CO_3 1:1:1, at 165°C without solvent.

We tried to replace K_2CO_3 by sodium methylate; the reaction was performed both at room temperature and at heating varying the molar ratio of the reagents. This resulted only in transesterification and in obtaining methyl 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**XII**) in 43% yield.

Compound **XII** was introduced into the reaction with dimethylacetylcarbinol in the presence of K_2CO_3; the best yield of compound **III** (50%) was obtained at the molar ratio compound **XII**–diethyl malonate–K_2CO_3 1:1.5:1, at 180°C within 7 h.

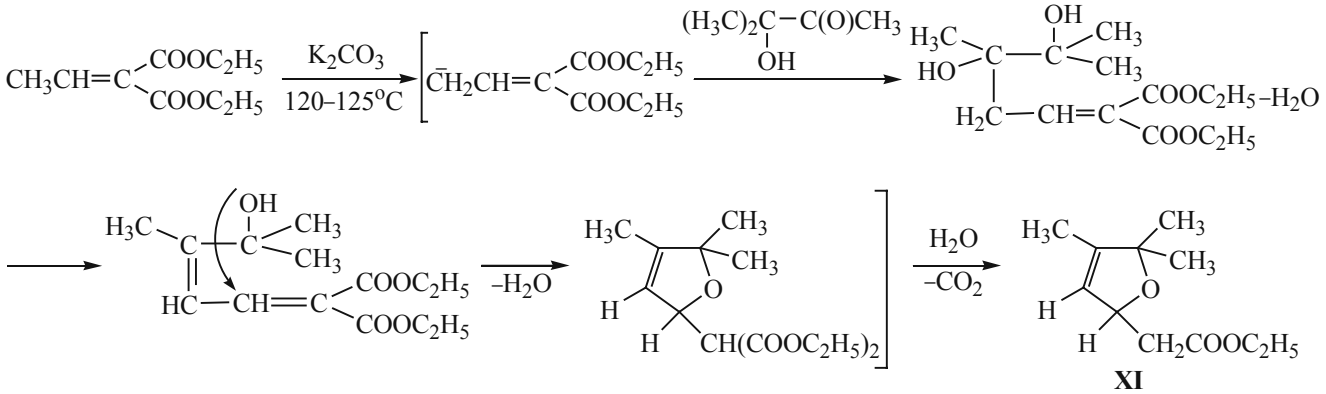
From 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carbonitrile (**XIII**) in the presence of K_2CO_3 like in the previous cases at various molar ratios of reagents, different temperature modes (from 120 to 180°C) and different time of heating compound **III** formed in moderate yields (from 20 to 32%). Consequently, the presence of a functional group in the position *3* of the 2-oxodihydrofuran ring favored the reaction to proceed along the above pathway resulting in the formation of compound **III**.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Specord 75IR from mulls in mineral oil. ^{1}H NMR spectra were registered on a spectrometer Varian Mercury 300 (300 MHz), internal reference TMS. Mass spectra were obtained on an instrument MKh-1321A, electron impact, energy of ionizing electrons 50–70 eV, direct admission of samples into the ion source. The purity of synthesized compounds was checked by TLC on Silufol UV-254 plates, eluent acetone–benzene, 1:2, development in iodine vapor or under UV radiation. Melting points were measured on a Boëtius heating block.

2,2,3,6,6-Pentamethyl-1,7-dioxaspiro[4.4]non-3-en-8-one (III). *a*. To 8 g (0.05 mol) of diethyl malonate was added 13 g (0.1 mol) of K_2CO_3 and 10.2 g (0.1 mol)

Scheme 2.



XI

of dimethylacetylcarbinol. The reaction mixture was heated at 140–150°C for 10 h, on cooling it was acidified with 10–15% hydrochloric acid till pH 3–4, and the stirring was continued for 30 min more. The reaction products were extracted into ether, and the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. We obtained 1.2 g (20%) of compound **II**, bp 81–83°C (2 mm Hg), 1.3 g (15%)of compound **I**, bp 127–129°C (2 mm Hg), and 4.7 g (45%) of compound **III**, bp 160–165°C (2 mm Hg), mp 113°C (from hexane). IR spectrum, cm^{-1}: 1770 (C=O lact), 1660 (C=C). ^1H NMR spectrum (DMSO-*d*), δ, ppm: 1.10 s (12H), 1.60 d (3H, *J* 2 Hz), 2.2 d and 2.8 d (2H, *J* 18 Hz), 5.15 q (1H, *J* 2 Hz). Mass spectrum, *m/z* (I_{rel}, %): 210 (5) $[M]^+$, 193 (3), 182 (11), 153 (22), 137 (14), 124 (100), 109 (94), 95 (10), 81 (16), 79 (13), 67 (16). Found, %: C 68.42; H 8.60. $C_{12}H_{19}O_3$. Calculated, %: C 68.57; H 8.57.

b. To 19.8 g (0.1 mol) of compound **I** was added 13.8 g (0.1 mol) of K_2CO_3 and 12 g (0.1 mol) of dimethylacetylcarbinol. The reaction mixture was heated for 7–8 h, on cooling it was acidified with diluted (1:1) hydrochloric acid till pH 3–4, and the stirring was continued for 30 min more. The reaction products were extracted into ether, and the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. Yield 50%.

c. To 1.7 g (0.1 mol) of 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid was added 13.8 g (0.1 mol) of K_2CO_3 and 12 g (0.1 mol) of dimethylacetyl-carbinol. After the treatment described in procedure *b* we obtained 0.4 g (2%) of compound **III**.

d. To methyl 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**XII**) was added K_2CO_3 and dimethylacetylcarbinol in a ratio 1:1:1.5. The reaction mixture was heated for 7 h at 180°, on cooling it was acidified with diluted (1:1) hydrochloric acid. The reaction products were extracted into ether, and the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. Yield 50%.

e. To 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carbonitrile (**XIII**) was added K_2CO_3 and dimethylacetylcarbinol in a ratio 1:1:1.5. The reaction mixture was heated for 7 h at 180°, on cooling it was acidified with diluted (1:1) hydrochloric acid. The reaction products were extracted into ether, and the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. Yield 32%.

Physicochemical constants and spectra of compound **III** obtained by procedures *a*–*e* were identical.

19-Methyl-7,15-dioxatrispiro[5.1.0.5.3.2]-nonadec-18-en-16-one (VII). To 8.0 g (0.05 mol) of diethyl malonate was added 13.0 g (0.1 mol) of K_2CO_3 and 14.4 g (0.1 mol) of 1-acetylcyclohexanol. The reaction mixture was heated at 140–150°C for 10 h, on cooling it was acidified with 10–15% hydrochloric acid till pH 3–4, and the stirring was continued for 30 min more. The reaction products were extracted into ether, and the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. We obtained 1.9 g (24%) of 4-methyl-1-oxaspiro[4.5]dec-3-en-2-one (**VI**), bp 98–100°C (1 mm Hg), 1.3 g (12%) of ethyl 4-methyl-2-oxo-1-oxaspiro-[4.5]dec-3-ene-3-carboxylate (**V**), bp 154–155°C (1 mm Hg), and 5 g (35%) of compound **VII**, bp 220–225°C (1 mm Hg, calc.), mp 97–98°C (from hexane). IR spectrum, cm^{-1}: 1770 (C=O lact), 1660 (C=C). ^1H NMR spectrum (DMSO-*d*), δ, ppm: 1.20–1.90 m (20H), 2.00 d (3H, *J* 2 Hz), 2.95 d (2H, *J* 8 Hz), 5.40 q (1H, *J* 2 Hz). Mass spectrum, *m/z* (I_{rel}, %): 290 (6) $[M]^+$, 274 (3), 262 (10), 192 (25), 164 (100), 149 (45), 135 (11), 121 (93), 108 (93), 69 (95), 55 (44). Found, %: C 74.48; H 8.96. $C_{18}H_{26}O_3$. Calculated, %: C 74.48; H 8.96.

2,3,6-Trimethyl-2,6-diphenyl-1,7-dioxaspiro-[4.4]non-3-en-8-one (X). To 4.9 g (0.03 mol) of diethyl malonate was added 8.4 g (0.06 mol) of K_2CO_3 and 10 g (0.06 mol) of methylphenylacetylcarbinol. The reaction mixture was heated at 140–150°C for 10 h, on cooling it was acidified with 10–15% hydrochloric acid till pH 3–4, and the stirring was continued for 30 min more. The reaction products were extracted into ether, and the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. We obtained 1.9 g (33%) of dimethyl-5-phenylfuran-2(5*H*)-one (**VIII**), bp 145–147°C (2 mm Hg), n_D^{20} 1.5430, 0.5 g (6%) of ethyl 4,5-dimethyl-2-oxo-5-phenyl-2,5-dihydrofuran-3-carboxylate (**IX**), bp 175–177°C (2 mm Hg), n_D^{20} 1.5355, and 3 g (30%) of compound **X**, bp 220–222°C (2 mm Hg), mp 159°C (from hexane). IR spectrum, cm^{-1}: 3100 (=C–H), 1760 (C=O lact), 1660 (C=C), 950, 995 [δ(C–H_{arom})]. ^1H NMR spectrum (DMSO-*d*), δ, ppm: 0.64 s (3H, CH_3), 1.63 d (3H, =CCH_3, *J* 1.5 Hz), 1.78 s (3H, CH_3), 2.55 d (1H, ^2J 2 Hz) and 3.25 d (1H,CH, ^2J 17.3 Hz), 5.77 q (1H, =CH, *J* 1.5 Hz), 7.14–7.38 m (10H, C_6H_5). Found, %: C 79.45; H 6.41. $C_{22}H_{22}O_3$. Calculated, %: C 79.04; H 6.59.

Ethyl 2-(4,5,5-trimethyl-2,5-dihydrofuran-2-yl)acetate (XI). To 5.5 g (0.03 mol) of diethyl ethylidenemalonate was added 4.1 g (0.03 mol) of K_2CO_3 and 3.6 g (0.03 mol) of dimethylacetylcarbinol. The reaction mixture was heated at 140–150°C for 10 h, on cooling it was acidified with 10–15% hydrochloric acid till pH 3–4, and the stirring was continued for 30 min more. The reaction products were extracted into ether, and the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. Yield 3.7 g (64%), bp 155–160°C (20 mm Hg), n_D^{20} 2.5010. IR spectrum, cm^{-1}: 1725 (C=O ester), 1630 (C=C), 950, 995 [δ(C–H_{arom})]. ^1H NMR spectrum (DMSO-*d*), δ, ppm: 0.95–1.25 m (9H), 2.00–2.25 m (6H), 4.10 q (2H, *J* 5.5 Hz), 5.60–5.75 m (4H). Found, %: C 67.50; H 7.55. $C_{11}H_{18}O_3$. Calculated, %: C 67.69; H 7.69.

Methyl 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate (XII). To a solution of sodium methylate in anhydrous methanol was added first compound **I** and then dropwise dimethylacetylcarbinol. The reaction mixture was stirred at 80–85°C for 12 h (or the mixture was left standing at room temperature for 18 h). Then the reaction mixture was acidified with 10% acetic acid, the products were extracted with ether, and the extract was dried with magnesium sulfate. After distilling off the solvent the residue was distilled in a vacuum. Yield 43%, bp 135–138°C (2–3 mm Hg), mp 47–48°C (from hexane). IR spectrum, cm^{-1}: 1780 (C=O lact.), 1730 (C=O ester), 1640 (C=C), 1250 (C–O–C). Found, %: C 58.61; H 6.45. $C_9H_{12}O_4$. Calculated, %: C 58.69; H 6.52.

REFERENCES

1. Avetisyan, A.A. and Dangyan, M.T., *Usp. Khim.,* 1977, vol. 46, p. 1250.
2. Avetisyan, A.A., Tatevosyan, G.E., Mangasaryan, Ts.E., Matsoyan, S.G., and Dangyan, M.T., *Zh. Org. Khim*., 1970, vol. 6, p. 962.
3. Avetisyan, A.A., Ovsepyan, V.V., and Tokmadzhyan, G.G., *Khim. Geterotsikl. Soedin*., 1986, p. 1426.
4. Avetisyan, A.A. and Tokmadzhyan, G.G., *Arm. Khim. Zh.,* 1993, p. 219.
5. Avchibasi, H., Anil, H., and Toprak, M., *Phytochem*., 1987, vol. 26, p. 2852.
6. Itakava, H., Morita, H., Osava, K., Watanabe, K., and Itaka, Y., *Chem. Pharm. Bull.,* 1987, vol. 35, p. 2849.
7. Yamasaki, M., Okuyama, E., and Macbagashi, Y., *Chem. Pharm. Bull*., 1979, vol. 27, p. 1611.
8. Knoevenagel, E., *Ber.,* 1898, vol. 31, p. 2585.