

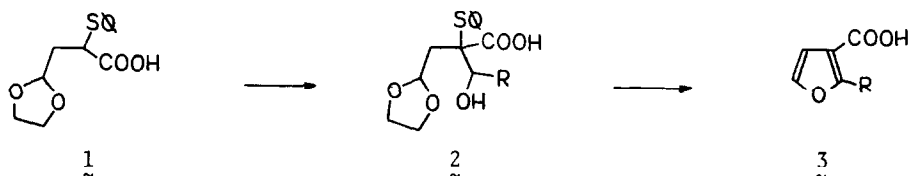
A SYNTHESIS OF 2-ALKYL-3-FUROIC ACIDS

Marcus A. Tius* and Selvaraj Savariar
Department of Chemistry, University of Hawaii,
Honolulu, Hawaii 96822, U.S.A.


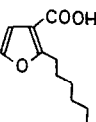
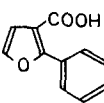
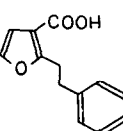
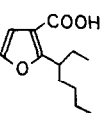
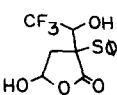
Abstract: An efficient synthesis of 2-alkyl-3-furoic acids has been developed. Addition of the lithium dianion of 4-oxo-2-phenylthiobutanoic acid ethylene acetal to aldehydes followed by acid-catalyzed cyclization produces furan products in high yield.

During the course of work directed toward the total synthesis of a natural product, the need for a connective synthesis of 2-alkyl-3-furoic acids presented itself. An obvious and convenient method for this synthetic transformation has been described by Knight.¹ The lithio dianion of 3-furoic acid is easily generated and its reaction with aldehydes and ketones takes place in high yield. The dianion is also known to react in high yield with iodomethane but more highly substituted alkylating agents fail to react with this nucleophile; the reaction with iodoethane has been reported to take place in only 42% yield.¹ The reaction conditions were varied in an unsuccessful attempt to improve the yield.² Inspection of the chemical literature failed to reveal a general method for preparing furoic acids of the desired substitution pattern,³ but published syntheses of 3-alkyl-⁴ and 3-acylfurans⁵ suggested a solution to the problem. The description of an efficient general method for the preparation of 2-alkyl-3-furoic acids follows.

The hydrolysis of ethyl-4-oxo-2-phenylthiobutanoate ethylene acetal⁶ with aqueous sodium hydroxide in methanol produced thiophenylcarboxylic acid 1 as a stable oil. The dianion of 1⁷ was generated with *tert*-butyllithium and was allowed to react with a series of



aldehydes. Treatment of the diastereomeric mixture of secondary alcohols 2 with acid led directly to alkyl furoic acids 3. The utility of this method has been demonstrated by preparing furans 4-8.^{8-12,13} The method fails with α,β -unsaturated aldehydes. For

					
~ 4	~ 5	~ 6	~ 7	~ 8	~ 9
Method A: 74%	76%	52%	73%	76%	
Method B: 71%	71%	50%	--	--	

(yields are overall for dianion addition and cyclization)

example, the reaction of the dianion of 1 with 3-methyl-2-butenal proceeded in high yield but the acid-catalyzed cyclization failed to produce the corresponding furoic acid, probably due to acid-catalyzed decomposition of the vinyl furan product. The dianion of 1 was allowed to react with trifluoroacetaldehyde;¹⁴ the product (95% yield) when treated with acid produced a labile mixture of diastereomers of 9.¹⁵ The trifluoromethyl group attenuates the nucleophilicity of the secondary alcohol to such an extent that the carboxyl group is able to compete for the electrophilic aldehyde carbonyl group. With the exception of α,β -unsaturated and highly electrophilic aldehydes, all others were effective substrates for the cyclization and this method should prove to be a useful addition to the known furan syntheses. Representative experimental procedures follow.

Dianion addition to aldehydes. A solution of 2 mmol of acid 1 in 10 ml of dry ether was treated with 2.2 equiv of *tert*-butyllithium at -78°C . A colorless precipitate appeared immediately. The precipitate was redissolved by slow addition of 10 ml of dry THF. The solution was warmed to -30°C during 1h to complete formation of the dianion. The solution was cooled to -78°C and 1.2 equiv of aldehyde was added. After 10 min at -78°C the reaction was quenched by addition of aqueous sodium hydroxide. The aqueous solution was extracted with ether and the ethereal layer was discarded. The aqueous layer was acidified with 1N aqueous HCl and was extracted with three portions of chloroform. The organic layer was dried (MgSO_4) and was concentrated to produce adduct 2 (92%-95% yield) which was used for the following step without purification.

Furan Cyclization. Method A: A solution of 1 mmol of adduct 2 in 20 ml of THF containing 430 μl of 70% aqueous perchloric acid was heated to reflux for 6h. The reaction mixture was allowed to cool to 25°C and was basified with 1N aqueous sodium hydroxide. The product was extracted once with ether and the ether extract was discarded. The aqueous phase was acidified with 1N aqueous HCl and was extracted with three portions of dichloromethane. Drying (MgSO_4) followed by solvent evaporation furnished the crude product. Flash chromatography on silica gel (33% ethyl acetate in hexane) produced pure product. Method B: A slurry of 9g of silica gel (230-400 mesh) in 30 ml of dichloromethane, 1 ml of 10% aqueous

oxalic acid and 1 mmol of adduct 2 was stirred at 25°C for 4h. The silica gel was filtered from the product and was washed thoroughly with dichloromethane. The combined washings were dried (MgSO_4) and were concentrated to produce an oily cyclic hemiacetal.

The intermediate product was dissolved in 20 ml of dry benzene and was heated to reflux for 15 min in the presence of ca. 30 mg of p-toluenesulfonic acid. The reaction mixture was basified with 1N aqueous sodium hydroxide and was worked up as in Method A.

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References and Notes

1. D. W. Knight, Tetrahedron Lett., 469 (1979); D. W. Knight and A. P. Nott, J. Chem. Soc., Perkin I, 1125 (1981).
2. The dianion was generated with potassium diisopropyl amide both in the presence and in the absence of 18-crown-6; sodium hexamethyldisilylazide was also used. Reaction of the lithio dianion with butyl bromide failed to take place in the presence of lithium tetrachlorocuprate. M. A. Tius and S. Savariar, unpublished results.
3. For recent examples of furoic acid synthesis, see: (a) S. P. Tanis and D. B. Head, Tetrahedron Lett., 4451 (1984); (b) E. Wenkert, M. E. Alonso, B. L. Buckwalter and E. L. Sanchez, J. Am. Chem. Soc., 105, 2021 (1983); (c) J. S. Ballesteros, D. J. McPhee and D. H. Hernandez, Bull. Chim. Soc. France, II, 176 (1982); (d) S. M. Nolan and T. Cohen, J. Org. Chem., 46, 2473 (1981); (e) H. König, F. Graf and V. Weberndörfer, Ann., 668 (1981); (f) I. Moubarak and R. Vessiere, Synthesis, 52 (1980); (g) R. A. Kretchmer and R. A. Laitar, J. Org. Chem., 43, 4596 (1978); (h) H. Gotthardt, C. M. Weissshuhn and K. Dörhöfer, Chem. Ber., 111, 3336 (1978); (i) M. Asaoka, N. Sugimura and H. Takei, Chem. Lett., 171 (1977); (j) J. J. K. Novak, Coll. Czech. Chem. Comm., 40, 2855 (1975). (k) K. Inomata, M. Sumita and H. Kotake, Chem. Lett., 709 (1979); (l) H. Kotake, K. Inomata, H. Kinoshita, S. Aoyama and Y. Sakamoto, Heterocycles, 10, 105 (1978). See also D. Liotta, M. Saindane and W. Ott, Tetrahedron Lett., 2473 (1983).
4. K. Inomata, S. Aoyama and H. Kotake, Bull. Chem. Soc. Japan, 51, 930 (1978).
5. H. Kinoshita, Bull. Chem. Soc. Japan, 55, 3225 (1982).
6. Prepared in four steps from acrolein: (i) thiophenol; (ii) ethylene glycol, acid; (iii) n-BuLi; (iv) addition of the anion to ethyl chloroformate.
7. K. Iwai, M. Kawai, H. Kosugi and H. Uda, Bull. Chem. Soc. Japan, 50, 242 (1977); P. A. Grieco, C.-L. Wang and S. D. Burke, J. Chem. Soc., Chem. Commun., 537 (1975).
8. 2-isopropyl-3-furoic acid (4): ^1H nmr (100 MHz, CDCl_3) δ 7.20 (d, $J = 2$ Hz, 1H), 7.61 (d, $J = 2$ Hz, 1H), 3.79 (septet, $J = 6.5$ Hz, 1H), 1.21 (d, $J = 7$ Hz, 6H); ^{13}C nmr (75 MHz, CDCl_3) δ 169.77, 168.77, 140.41, 110.94, 110.76, 27.27, 20.64; ν (CH_2Cl_2) 1724, 1684, 1587 cm^{-1} ; mass spectrum (m/e) 154 (m), 139 ($m-\text{CH}_3$), 125, 121, 111, 95, 93, 79; calcd for $\text{C}_8\text{H}_{10}\text{O}_3$ 154.0630, found 154.0635.

9. 2-hexyl-3-furoic acid (5): ^1H nmr (300 MHz, CDCl_3) δ 7.26 (d, $J = 2$ Hz, 1H), 6.69 (d, $J = 2$ Hz, 1H), 3.02 (t, $J = 7.5$ Hz, 2H), 1.68 (m, 2H), 1.35 (br s, 6H), 1.89 (m, 3H); ^{13}C nmr (75 MHz, CDCl_3) δ 170.00, 164.95, 140.57, 112.47, 110.81, 31.48, 28.85, 27.85, 27.70, 22.52, 14.03; ir (CH_2Cl_2) 1732, 1688 cm^{-1} ; mass spectrum (m/e) 196 (m), 151, 139, 126, 125, 108, 97; calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3$ 196.1099, found 196.1095.
10. 2-phenyl-3-furoic acid (6): ^1H nmr (300 MHz, CDCl_3) δ 7.95 (m, 2H), 7.43 (m, 4H), 6.90 (d, $J = 2$ Hz, 1H); ^{13}C nmr (75 MHz, CDCl_3) δ 168.93, 158.87, 141.46, 129.63, 129.43, 128.63, 128.15, 113.25, 112.93; ir (CH_2Cl_2) 1734, 1686, 1217 cm^{-1} ; mass spectrum (m/e) 188 (m), 171, 131, 115, 114, 105, 89, 77; calcd for $\text{C}_{11}\text{H}_8\text{O}_3$ 188.0473, found 188.0456.
11. 2-(2-phenyl)ethyl-3-furoic acid (7): ^1H nmr (300 MHz, CDCl_3) 7.31-7.19 (m, 6H), 6.70 (d, $J = 1.7$ Hz, 1H), 3.33 (t, $J = 8$ Hz, 2H), 3.00 (t, $J = 8$ Hz, 2H); ^{13}C nmr (75 MHz, CDCl_3) δ 169.70, 163.52, 140.84, 140.65, 137.95, 128.35, 126.16, 112.88, 110.89, 34.05, 29.74; ir (CH_2Cl_2) 1730, 1684, 1601, 1267, 1217 cm^{-1} ; mass spectrum (m/e) 216 (m), 198, 188, 141, 125, 115, 91; calcd for $\text{C}_{13}\text{H}_{12}\text{O}_3$ 216.0786, found 216.0771.
12. 2-(1-ethyl)pentyl-3-furoic acid (8): All data refer to the methyl ester of 8. ^1H nmr (300 MHz, CDCl_3) δ 7.26 (s, 1H), 6.62 (s, 1H), 3.81 (s, 3H), 3.52 (q, 1H), 1.66 (m, 4H), 1.30-1.00 (m, 4H), 0.86-0.76 (m, 6H); ^{13}C nmr (75 MHz, CDCl_3) δ 165.49, 164.45, 140.29, 113.92, 110.21, 51.09, 39.28, 33.38, 29.59, 27.10, 22.60, 13.93, 11.85; ir (CH_2Cl_2) 2959, 2932, 2861, 1723, 1597, 1518, 1464, 1439, 1300, 1196, 741 cm^{-1} ; mass spectrum (m/e) 224 (m), 195 (m- CH_3CH_2), 193, 167 (m-Bu), 163, 139, 135; calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3$ 224.1412, found 224.1401.
13. Furoic acids 4, 5, 7 and 8 appear to be new compounds. A synthesis of 6 has been reported: Reference 3j.
14. Trifluoroacetaldehyde was prepared by addition of the commercially available (Aldrich) ethyl hemiacetal to concd sulfuric acid at 90°C. See N. Ishikawa, M. G. Koh, T. Kitazume and S. W. Choi, *J. Fluorine Chem.*, **24**, 419 (1984).
15. The following tentative assignments in the ^1H nmr (CDCl_3 , 300 MHz) spectra of the isomers of 9 have been made: Isomer A. δ 7.38-7.11 (m, 5H, SPh), 5.42 (dd, $J = 6$ Hz, < 1 Hz, 1H, OCH_2OH), 4.59 (dq, $J = 6$ Hz, 1 Hz, 1H, CHCF_3), 4.43 (br s, 1H, OH), 2.88 (dd, $J = 12$ Hz, 6 Hz, 1H, CHH), 2.59 (dd, $J = 12$ Hz, < 1 Hz, 1H, CHH). Isomer B. δ 7.41-7.11 (m 5H, SPh), 5.40 (dd, $J = 6$ Hz, < 1 Hz, 1H, OCH_2OH), 4.55 (m, 1H, CHCF_3), 3.95 (br d, $J = 6$ Hz, 1H, OH), 3.24 (dd, $J = 12$ Hz, 6 Hz, 1H, CHH), 2.44 (dd, $J = 12$ Hz, < 1 Hz, 1H, CHH).

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