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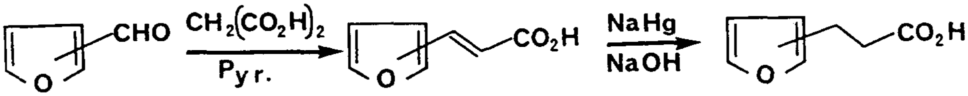
CYCLIZATIONS OF SOME FURYL ACID CHLORIDES

Edward J. Walsh, Jr.* and Guy B. Stone[1]
Department of Chemistry, Allegheny College
Meadville, PA 16335

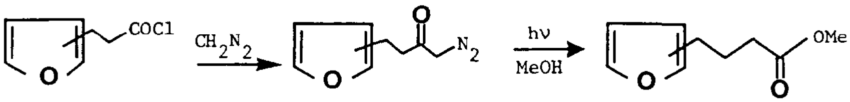
Abstract: Intramolecular Friedel-Crafts acylation of the furan ring has been accomplished in good yields with stannic chloride for both furyl isomers of butyryl acid chloride. The propionyl chloride isomers, however, failed to produce reasonable quantities of the cyclic ketone.

There appears to be a widespread occurrence of fused 5-membered heterocyclic ring systems in natural products.[2] A particularly direct entry into some of these is through intramolecular Freidel-Crafts acylation. While this approach is well known in thiophene systems,[3] little, if any, attention has been directed to the furan systems in this regard.[4] In fact, as the Tanis group points out,[5] there are few examples in the literature of any cationic cyclizations on the furan nucleus. In this communication we wish to report the results of our study of the Lewis acid catalyzed cyclization of certain furyl acid chloride derivatives.

Both the 3-(2 or 3-furyl) propionic acids were prepared by standard methods[6] from the corresponding aldehyde[7] and converted into the acid chloride by treatment with thionyl chloride. Each of these steps in several trials averaged between 76-98% yield.

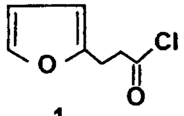
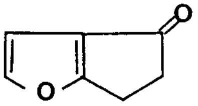
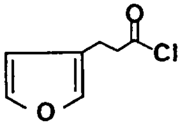
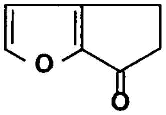
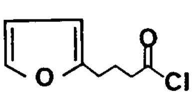
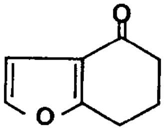
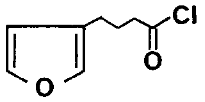
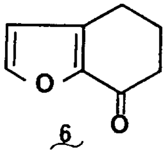


The 4(2 & 3-furyl) butanoic acids were prepared by converting the appropriate propionic acid chloride to the diazoketone and subjecting these compounds to a photo-Wolff



rearrangement.[8] The ester was then hydrolyzed with base. The overall yield from the propionyl chloride to the butyl ester derivative was 90%.

Table Intramolecular Friedel-Crafts Acylation on the Furan Nucleus Acid

Acid Chloride	Lewis Acid	Cyclized Ketone	% yield^a
 1	Et_2AlCl(-78°) $AlCl_3$(-23°)		0 0
 2	$SnCl_4$(0°) Et_2AlCl(-78°)		<4^b 0
 3	$SnCl_4$(0°) Et_2AlCl(-78°)	 5	70 17^c
 4	$SnCl_4$(0°) Et_2AlCl(-78°)	 6	90 60

[a] yields, except where noted, are isolated yields, analytically pure.

[b] not isolated or characterized

[c] crude yield

The results in the Table reveal some interesting features of this reaction. The acid chlorides 1 and 2 appear most reluctant to close to a 5-membered ring ketone under these conditions. Closure to a 5-membered ring using Lewis acid catalysis in furan systems has been a problem in other studies as well.[5,9] Reasons for this, involving the Lewis acid and the furan ring, have been advanced.[9]

The higher homologues 3 and 4 however, undergo cyclization to the 6-membered ring ketone smoothly and cleanly with stannic chloride. While no attempt was made to optimize the yields of the ketones from 3 and 4, they are nonetheless surprisingly good. One might expect the yield of 5 to be less than 6 given the difference in reactivity in electrophilic aromatic substitution between the 3- and the 2-position in furan.

The ketone 5, 4-oxo-4,5,6,7-tetrahydrobenzofuran[10] has been prepared by another method in 30% yield[11] and is the subject of a recent patent application.[12] Compound 6, 7-oxo-4,5,6,7-tetrahydrobenzofuran,[13] as far as we could ascertain, has not been reported.

These compounds 5 and 6 are apparently useful intermediates in the preparation of various drugs[12] and given the location of the keto groups should provide a convenient locus for further synthetic elaboration. Additional synthetic versatility is afforded these compounds through the behavior of the furan nucleus itself, in particular, oxidation.[14] These studies and other methods of cyclization are the subjects of current investigations in this laboratory.

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Footnotes:

1. American Chemical Society-Petroleum Research Fund Scholar.
2. F.M. Dean, Adv. Heterocyclic Chem. (1982) 30, 167
3. P. Cagniant, G. Merle and D. Cagniant, Bull. Soc. Chim. Fr. (1970) 322 and references therein.
4. For some examples of naturally occurring fused furan systems see M. Miyashita, T. Kumazawa and A. Yoshikoshi, J. Org. Chem. (1984) 49, 3728; R.P. Walker, R.M. Rosser, D.J. Faulkner, L.S. Bass, H. Cun-keng and J. Clardy, Ibid. (1984) 49, 5160; E. Wenkert, M.E. Alonso, B.L. Buckwalter and E.L. Sanchez, J. Amer. Chem. Soc. (1983) 105, 2021; P.A. Jacobi and D.G. Walker, Ibid. (1981) 103, 4611; C. Cimino, S. DeStefano, A. Guerriero and L. Minale, Tet. Letters (1975) 3723; D. Nasipuri and G. Das, J. Chem. Soc., Perkins I (1979) 2776; H. Stetter and R. Lauterback, Chem. Ber. (1960) 93, 603; M.E. Garst and T. Spencer, J. Org. Chem. (1983) 48, 2442.
5. S.P. Tanis and P.M. Herrinton, J. Org. Chem. (1983) 48, 4572 and references therein.
6. A.L. Mindzhoian, Ed., Synthesis of Heterocyclic Compounds, Vol. 2, Consultants Bureau, Inc., NY, Chapman and Hall, Ltd., London, 1959, p. 48.
7. Both the 2 and 3 furfurals are available from Aldrich Chemical Co.
8. K.B. Wiberg and L.K. Olli, J. Amer. Chem. Soc. (1980) 102, 7467.
9. S.M. Singh, S. Singh and R.B. Rao, Indian J. Chem. (1980) 19B, 320.
10. ^1H nmr ($CDCl_3$, 60 mHz) δ = 7.27 (d,J=1.5Hz,1H), 6.60 (d,J=1.5Hz,1H), 2.83 (t,J=5.5Hz,2H), 2.25 (m, 4H); IR (neat) 3130, 2940, 1670, 1590 cm^{-1}; Anal. Calcd. for $C_8H_8O_2$:C, 70.58, H, 5.92, Found: C, 70.26, H, 6.05.

11. E. Bisagni, J.P. Marquet, J. Andre-Louisfert, A. Cheutin and F. Feinte, Bull. Soc. Chim. Fr. (1967), 2796.
12. M. Matsumoto and N. Watanabe, European Patent Application, 83107630.2 (1983).
13. For the preparation of 6, a solution of 0.73 g (4.2 mmol) of the acid chloride, 4 and 5 ml of dry CH_2Cl_2 under N_2 was cooled to 0°. To this was added dropwise, with stirring, 1.4 g (5.5 mmol) of $SnCl_4$. After addition, the mixture was stirred at 0° for 2 h and then allowed to come to room temperature. To this mixture was added 60 ml of CH_2Cl_2, 4 g of ice then 10 ml of dilute HCl. The reaction mixture was then extracted with saturated NH_4Cl (3x) and then with a $NaHCO_3 \cdot NaCl$ solution. After drying over anhydrous $MgSO_4$, rotary evaporation gave .57 g (4.2 mmol) of a light yellow solid, m.p. 58-60.5°. Recrystallization from pet ether gave .51 g (3.8 mmol) of white needles, m.p. 60.5-61.5°. ^{1}Hnmr ($CDCl_3$, 60 mHz) δ = 7.60 (d,J=1.5Hz,1H), 6.45 (d,J=1.5Hz,1H), 2.50 (m, 6H); IR(KBr) 3100, 2930, 1650, 1590 cm^{-1}; ^{13}C-NMR: 186.0 (C-7), 147.6 (C-7a), 147.2 (C-2), 139.4 (C-3a), 111.4 (C-3), 38.1 (C-6), 24.3 (C-4), 22.8 (C-5); Anal. Calcd. for $C_8H_8O_2$: C, 70.58, H, 5.90. Found: C, 7.70, H, 5.95; m/e 136 (M^+), base peak 108 (M^+-CO).
14. A.R. Katritzky, et al., Eds. Adv. Heterocyclic Chem. (1982) 30, 167; Y.S. Rao, Chem. Rev. (1976) 76, 625 and references therein.

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