The Sonochemical Barbier Reaction Extended to Carboxylate Salts. An Easy Access to 2-Furanyl Ketones

M. J. Aurell,† C. Einhorn,‡ J. Einhorn,‡ and J. L. Luche*,†

Université P. Sabatier, Bat. 2R1, 118 route de Narbonne, 31062 Toulouse Cedex, France, and Université J. Fourier, Bat. Chimie, 38041 Grenoble Cedex, France

Received July 29, 1994

The 2-furanyl ketone moiety is found in a number of natural products,[1] as precursors to alcohols able to provide useful rearranged structures,[2] and in various chemicals of medicinal and agricultural interest.[3] Their access is generally considered as not very easy.[4] Diverse preparative routes, involving a Friedel–Crafts acylation of the furan ring,[1,5] oxidation of the corresponding alcohols,[4] and several organometallic reactions, have been described. Among the latter, syntheses starting from 2-furfuraldehyde, in three steps via the cyanohydrin–trimethylsilyl ether, lead to satisfactory yields of the desired compounds.[6] More straightforward methods performed under mild conditions make use of 2-furanyllithium or -magnesium reagents. Their addition to aldehydes in a vanadium-catalyzed coupling reaction,[7] or to acyl chlorides or carbonates in the presence of manganese(II) salts,[8] provides the expected compounds in convenient yields. Coupling of organocopper reagents with trifluoroacetic anhydride was applied to the preparation of 2-(trifluoroacetyl)furan,[9] and the reaction of organomercurials with acyl chlorides, although efficient, is less attractive due to the nature of the organometallics.[10]

Following the same principle as above, we found a simple method, which avoids the use of toxic auxiliaries, difficult reaction conditions, or multistep procedures, by using an extension of the Barbier procedure[11] to carboxylate salts. In a previous work, we determined that high yields of ketones, uncontaminated by the corresponding tertiary alcohol, can be obtained by sonication of a mixture of a lithium carboxylate, an alkyl chloride, and lithium in THF at room temperature (eq 1).[12] Since the formation of the intermediate organolithium reagent and deprotonation of various acidic compounds are very rapid under such conditions,[13] attempts were made to use this procedure in the direct *in situ* preparation and condensation of 2-furanyllithium with carboxylates in a one-pot sequence. The general route is shown in eq 2 and the "reaction cascade" represented in Scheme 1.

Scheme 1

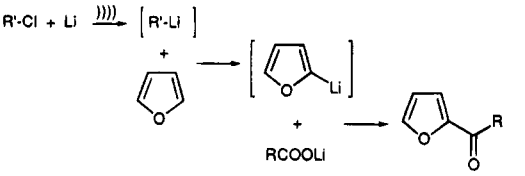
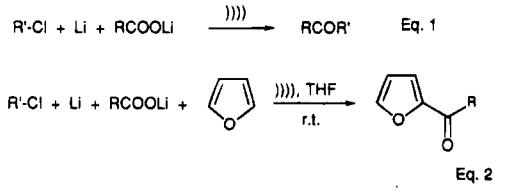


Table 1. 2-Furanyl Ketones from Lithium Carboxylates and *in-Situ* Generated 2-Furanyllithium Reagents

carboxylate	furanic compd	product (% yield)[a]	lit. yield[ref]
3-methylbutyrate	**1a**	**2a** (76)	*b*
	1b	**2b** (74)	66[c]
4-pentenoate	**1a**	**3a** (75)	80[d]
	1b	**3b** (78)	
benzoate	**1a**	**4a** (77)	90[e]
	1b	**4b** (78)	92[e]
	5	**6** (52)	

[a] Isolated yields of purified compounds. The spectral and analytical data of the compounds prepared in this work are in agreement with the structures. [b] See ref 3a. [c] Via a Friedel–Crafts acylation. See ref 1. [d] From furfuraldehyde cyanohydrine trimethylsilyl ether. See ref 6. [e] Via acylation of the corresponding 2-furanyl organomercurial. See ref 10.



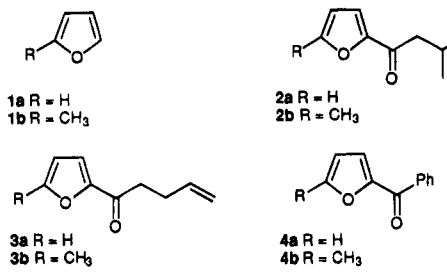
Critical parameters for the success of the procedure are the choice of the alkyl chloride and the composition of the metal. *tert*-Butyl chloride proves to be suitable for several reasons. Under sonication, it gives *tert*-butyllithium in a very rapid process. The basicity of the latter makes the formation of 2-furanyllithium very efficient,[13] and its steric crowding slows down its addition to the carboxylate. Lithium with 1–2% sodium content is necessary, as the low sodium alloy usually remains unattacked. The reactions are performed at room temperature using a simple ultrasonic cleaning bath,[14] and a typical procedure is as follows. A mixture of furan (5 equiv), lithium carboxylate (1 equiv), *tert*-butyl chloride (1.5 equiv), and lithium (3 equiv) in dry THF are sonicated (bath: Kerry Pulsatron, 38 kHz thermostated at 15–18 °C) for 10–15 min, until the metal is consumed. Hydrolysis (aqueous saturated NH_4Cl) and workup as usual in organometallic syntheses give a crude mixture which is purified by column chromatography. The desired compounds are obtained in synthetically useful

† Université P. Sabatier.
‡ Université J. Fourier.

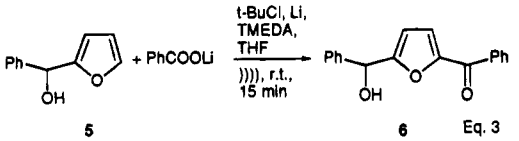
(1) Scholz, S.; Marschall-Weyerstahl, H.; Weyerstahl, P. *Liebigs Ann. Chem.* **1985**, 1935–1950.
(2) For the rearrangement of 1-(2-furyl)carbinols, see: Castagnino, E.; D'Auria, M.; De Mico, A.; D'Onofrio, F.; Piancatelli, G. *J. Chem. Soc., Chem. Commun.* **1987**, 907–908 and references cited therein.
(3) (a) Kondo, M.; Minai, M.; Kay, S.; Higashi, T.; Ueda, Y *Eur. Pat. Appl.* EP 268 820; *Chem. Abstr.* **1989**, *109*, 170222k. (b) Uchida, M.; Komatsu, M.; Morita, S.; Kanbe, T.; Yamasaki, K.; Nakagawa, K. *Chem. Pharm. Bull.* **1989**, *37*, 958–961.
(4) Antonioletti, R.; Arista, L.; Bonadies, F.; Locati, L.; Suttri, A. *Tetrahedron Lett.* **1993**, *34*, 7089–7092.
(5) Fayed, S.; Delmas, M.; Gaset, A. *J. Mol. Catal.* **1985**, *29*, 19–31.
(6) Fischer, K.; Hünig, S. *J. Org. Chem.* **1987**, *52*, 564–569.
(7) Hirao, T.; Misu, D.; Agawe, T. *J. Am. Chem. Soc.* **1985**, *107*, 7179–81.
(8) Friour, G.; Cahiez, G.; Normant, J. F. *Synthesis* **1985**, 50–54.
(9) Kerdesky, F. A. J.; Basha, A. *Tetrahedron Lett.* **1991**, *32*, 2003–2004.
(10) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem.* **1989**, *365*, 379–387.
(11) For a recent comprehensive account on this reaction, see : Blomberg, C. *The Barbier Reaction and Related One-step Processes;* Springer-Verlag: Berlin, 1993.
(12) Danhui, Y.; Einhorn, J.; Einhorn, C.; Aurell, M. J.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1994**, 1815–1816.
(13) J. Einhorn, J. L. Luche *J. Org. Chem.* **1987**, *52*, 4124–4126.
(14) For a proper use of ultrasonic cleaning baths in chemistry, see: Mason, T. J. *Practical Sonochemistry*; Ellis Horwood: London, 1991; pp 52–72.

0022-3263/95/1960-0008$09.00/0

yields, which compete favorably with literature methods. The undesired tertiary alcohols resulting from the double addition of the lithium reagent are generally formed in low amounts, less than a few percent. Other compounds present in the reaction mixture consist mostly of the unreacted acid and polar unidentified byproducts. Examples are given in Table 1.



The above examples show that saturated, unsaturated, and aromatic carboxylates can be successfully used in the method. Limitations were found with α,β-unsaturated carboxylates. Reactions using lithium acrylate or crotonate, the solubility of which is very low in THF, lead to the recovery of the acid, up to 60%, and the neutral fraction consists of a complex mixture from which only 20−30% of the desired ketones can be isolated. In an attempt to use a functionalized furan derivative, alcohol **5** (eq 3) was prepared according to the published sonochemical procedure.[13] It was reacted (2 equiv) as described above, in the presence of tetramethylethylenediamine (TMEDA), with lithium benzoate, to give the 2,5-disubstituted furanyl keto alcohol **6** in 52% isolated yield,



5 **6** Eq. 3

along with 13% of pivalophenone, resulting from some addition of *tert*-butyllithium to lithium benzoate. The regioselectivity in favor of the metalation at position 5 of the ring is in agreement with previous reports.[15]

Despite some limitations, the method should be applicable to the synthesis of a number of useful compounds. Its ease and rapidity constitute valuable advantages, which will be examplified in further developments of this work.[16]

Acknowledgment. The authors wish to thank the EEC (Human Capital and Mobility) for a fellowship (to M.J.A.)

Supplementary Material Available: Experimental procedure, IR, ^{1}H and ^{13}C NMR spectra of 1-(2-furanyl)-3-methyl-1-butanone (**2a**), 1-[2-(5-methylfuranyl)]-4-pentene-1-one (**3b**), and [2-[5-(1-phenylhydroxymethyl)furanyl]] phenylmethanone (**6**) (11 pages).

JO941251R

(15) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104−109 and references cited therein.

(16) A few attempts were made to generate *in situ* other useful, not readily accessible organolithium reagents. Benzyllithium is obtained by deprotonation of toluene and condensed with lithium benzoate in 68% yield, but thiophene and pyrrole remain unreactive.