

METHYL AND n-ALKYL KETONES FROM CARBOXYLIC ACID CHLORIDES  
AND ORGANOCOPPER REAGENTS

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Lithium diorganocopper reagents, represented as  $R_2CuLi$ , have recently been shown to effect selective replacement of halogen by R in a wide variety of organic halides<sup>2</sup> and have been used effectively in the stereospecific synthesis of several natural products.<sup>3</sup> We report now that lithium dimethyl- and di-n-alkylcopper reagents react cleanly and under extremely mild conditions with a wide range of carboxylic acid chlorides forming the corresponding methyl and n-alkyl ketones in excellent yields (Eq. 1).<sup>4</sup>



Ethereal solutions of the organocopper reagents were easily prepared at 0° under nitrogen<sup>5</sup> from the reaction of methyl-, ethyl-, or n-butyllithium with cuprous iodide<sup>6</sup> (molar ratio 2:1) and were cooled after 5-10 min at 0° to -78°. All of the alkylations were performed at -78° for 15 min with 3 moles of the copper reagent (concentration ca. 0.25 M) per mole of acid chloride<sup>7</sup> and were quenched at -78° with methanol. Products were analyzed by vapor phase chromatography, isolated, and characterized by comparison with authentic samples.<sup>8</sup> The transformations which have been achieved using lithium dimethyl-, diethyl-, and di-n-butylcopper and substrates carefully selected to represent primary, secondary, tertiary and aryl acid chlorides are summarized in Table I.

Table I. Reaction of Lithium Diorganocopper Reagents,  $R_2CuLi$ , with Acid Chlorides (Eq. 1) in Ether at  $-78^\circ$ .

Entry	Acid Chloride	R, % Yield <sup>a</sup>	
		$CH_3$	$n-C_4H_9$
1	$n-C_5H_{11}COCl$	81	79
2	Cyclo- $C_6H_{11}COCl$	86	80(71) <sup>b</sup>
3	$(C_6H_5)_2CHCOCl$	93 <sup>c</sup>	90 <sup>c</sup> (80 <sup>c</sup> )
4	$t-C_4H_9COCl$	84	90
5	3,5- $(CF_3)_2C_6H_3COCl$	92 <sup>c</sup>	75-80 <sup>c</sup>
6	$p-O_2NC_6H_4COCl$	50 <sup>c</sup>	--

<sup>a</sup>Yield determined by quantitative vpc analysis, unless otherwise noted.

<sup>b</sup>Yield in parenthesis refers to case to  $R = C_2H_5$ .

<sup>c</sup>Yield of isolated product.

Under the same conditions used for the organocopper alkylations, organolithium reagents themselves are totally unsatisfactory for converting acid chlorides into ketones, tertiary alcohols being the expected and observed major products;<sup>9</sup> thus the reactive species in this ketone syntheses is not an organolithium compound.

No appreciable amounts of by-products were observed in most instances, and the crude ketonic products usually had spectral properties identical with those of authentic samples. Only *p*-nitrobenzoyl chloride gave a water-soluble and as yet unidentified side-product which became the major product in the butylation reaction, even when this alkylation was run at  $-95^\circ$  for 3 min.<sup>10,11</sup>

Comparison of other generally effective reagents for ketone formation from carboxylic acid derivatives shows that lithium diorganocopper reagents are equally useful in most instances and occasionally more useful for substrates subject to competing side reactions. Thus organocadmium and zinc reagents transform arylacetyl chlorides into the corresponding ketones in highly variable yields,<sup>12</sup> and organoaluminum reagents tend to cause substantial Friedel-Crafts acylation of aromatic rings in most aryl acid chlorides<sup>13</sup> (compare entries 3, 5 and 6 in Table I). Organolithium reagents convert *p*-nitrobenzoic acid to polymer and often cause undesired metalation of  $\alpha$ -aryl

alkanoic acids and of benzoic acids bearing strongly electron withdrawing groups<sup>14</sup> (compare entries 6, 3, and 5 in Table I).

Carbonyl or halogen functional groups in the acid chloride molecule would probably be inert to lithium diorganocopper reagents under the extremely mild conditions used for conversion of acid chloride to ketone.<sup>15</sup> Such selective alkylation of functionalized acid chlorides as well as extension of the ketone synthesis reported here to secondary and tertiary alkyl ketones are being investigated.

Although this organocopper ketone synthesis is limited thus far to acid chloride coupling with primary alkyl groups and to readily available organolithium compounds,<sup>16</sup> the use of lithium diorganocopper reagents to replace chlorine by methyl or *n*-alkyl in various types of acid chlorides is a straightforward and general synthetic method.

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3. (a) Farnesol: E.J. Corey, J.A. Katzenellenbogen, and G.H. Posner, *ibid.*, **89**, 4245 (1967); (b) Insect juvenile hormone: E.J. Corey, J.A. Katzenellenbogen, N.W. Gilman, S.A. Roman, and B.W. Erickson, *ibid.*, **90**, 5618 (1968); (c) Carvestrene: O.P. Vig, J.C. Kapur, and S.D. Sharma, *J. Indian Chem. Soc.*, **45**, 1026 (1968); and (d) Fulvopulmierin: G. Buchi and J.A. Carlson, *J. Amer. Chem. Soc.*, **91**, 6470 (1969).
4. (a) We have found the corresponding monoalkylcopper reagents, RCu, to be less effective than the lithium diorganocopper reagents in these transformations: cf. H. Gilman and J. M. Straley, (*Rec. Trav. Chim.*, **55**, 821 (1936)) for phenylcopper conversion of acetyl and benzoyl chlorides into the corresponding phenyl ketones in 54-55% yields, and A.E. Jukes, S.S. Dua and H. Gilman (*J. Organometal. Chem.*, **21**, 241 (1970)) for reaction of polyhaloaryl-copper reagents and acid chlorides; (b) lithium dimethylcopper was first observed to react with benzoyl chloride forming acetophenone in 76% yield by G.M. Whitesides, C.P. Casey, J. San Filippo, Jr., and E.J. Panek, *Trans. N.Y. Acad. Sci.*, **29**(5), 572 (1967); (c) for a recent, preliminary study of lithium diorganocopper reagents and acid chlorides, see C. Jallabert, N.T. Luong-Thi and H. Riviere, *Bull. Soc. Chim. Fr.*, **1970**, 797; (d) for reaction of acetylenic copper reagents with acid chlorides, see J.F. Normant and M. Bourgain, *Tetrahedron Lett.*, 2659 (1970).
5. All reactions involving organocopper reagents were carried out with the usual precautions for rigorous exclusion of air and moisture.

6. Cuprous iodide was purchased from Eastman Organic Chemicals and was used without purification. The organolithium reagents were purchased from Foote Mineral Co.; ethyllithium in benzene and *n*-butyllithium in pentane were used.
7. Typically reactions were run using from 1 to 2 mmoles of acid chloride, indicating that synthetically useful amounts of ketone can be produced in this way.
8. Characterizations were achieved using infrared, nuclear magnetic resonance and, for new compounds, elemental microanalysis, in addition to vapor chromatographic data.
9. (a) For kinetics of organolithium addition to ketones see S.G. Smith, Tetrahedron Lett., 6075 (1966); (b) for the low temperature addition of *t*-butyllithium to hexamethylacetone see P.D. Bartlett and E.B. Lefferts, J. Amer. Chem. Soc., 77, 2804 (1955).
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