Notes

Direct, Low Temperature, *in Situ* Nucleophilic Aroylation with Aroyllithium Reagents

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Introduction

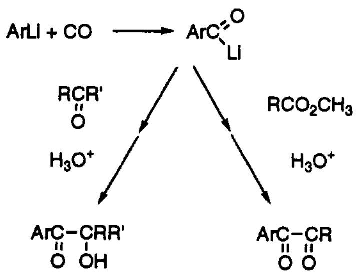
Our previous studies of the low temperature, *in situ* RLi/CO systems have shown them to be applicable to the direct nucleophilic acylation of aldehydes and ketones,[1] esters,[2] heterocumulenes,[3] and organic disulfides.[4] In this work we used *n*-, *sec*- and *tert*-butyllithium as representative alkyllithium reagents, but studies using chlorosilanes as the electrophiles showed that other alkyllithiums worked equally well in the acylation reaction.[5]

To complement the investigations of alkyllithium/CO systems, we have conducted a study using aryllithium/CO systems. The expected chemistry is shown in Scheme I.

Much of the prior work of others relating to attempted nucleophilic aroylation by ArLi/CO has focused on such reactions of phenyllithium. The earliest report was one by Wittig[6] that the reaction of phenyllithium with CO gave, upon hydrolysis, $PhC(O)CHPh_2$ in unspecified yield. Some years later, Jutzi and Schröder[7] investigated the same reaction and confirmed the formation of $PhC(O)CHPh_2$ in 86% yield. Whitesides and his co-workers[8] conducted a detailed study of the PhLi/CO reaction. Although no useful synthetic chemistry resulted from these studies, the complicated reactions which occur when solutions of phenyllithium are carbonylated were well delineated. More recently, Nudelman and her co-workers have continued studies of the aryllithium/CO reagent system, and some useful synthetic procedures have been developed. Thus, the reaction of aryllithium with CO in the presence of alkyl bromides at -78 °C gave alkyldiarylcarbinols in good yield.[9] Presumably, alkylation of the ArC(O)Li intermediate, followed by ArLi addition to the ketone thus formed, had taken place. Also, hindered aryllithiums such as α-naphthyllithium and (2,6-dimethylphenyl)lithium were found to react with CO (in the absence of an electrophilic substrate) to give 1,2-diketones, ArC(O)C(O)Ar.[10]

In our investigation we have applied the direct, *in situ* nucleophilic acylation procedure, which was so successful with alkyllithium/CO systems, to ArLi/CO systems. The aryllithiums studied were phenyllithium, *p*-tolyllithium, *o*-tolyllithium, (2,6-dimethylphenyl)lithium, and mesityllithium [(2,4,6-trimethylphenyl)lithium], using as electrophilic substrates pivalaldehyde, ketones, and esters. The results are of some interest, although they are of limited preparative utility.

Scheme I



Results and Discussion

In the RLi/CO low temperature, *in situ* reagent system, in which the electrophilic substrate and carbon monoxide compete for the organolithium reagent as it is added, products derived from RLi or RC(O)Li, or from both, with the electrophile can be obtained. In the case of phenyllithium, in the absence of exceptional steric hindrance in the electrophile, only products derived from phenyllithium were obtained. Thus the PhLi/CO system, used in situ at -110 °C with $C_6H_5CO_2Me$ gave only $(C_6H_5)_2CO$ in 94% yield. With benzophenone only $(C_6H_5)_3COH$ was obtained in 80% yield, and $(Me_2CH)_2CO$ gave $PhC(OH)(CHMe_2)_2$ (84%).

In situ reaction of PhLi, CO, and Me_3CCO_2Me, in which the C=O group is more hindered, gave an 11% yield of the acylation product, $C_6H_5C(O)C(O)CMe_3$, but phenyllithium trapping by the ester was the major process, giving $C_6H_5C(O)CMe_3$ in 61% yield. When the steric hindrance was increased to include the alkoxy group, i.e., by using $Me_3CCO_2CMe_3$ as the electrophile, the acylation product, $C_6H_5C(O)C(O)CMe_3$, predominated (45% yield), but now $C_6H_5C(O)C(O)C_6H_5$ (25% yield), indicative of a slow $C_6H_5C(O)Li$/substrate reaction, also was formed. A very hindered ketone, $(Me_3C)_2CO$, reacted with the C_6H_5Li/CO reagent system to give only the acylation product, $C_6H_5C(O)C(OH)(CMe_3)_2$, in 75% yield.

p-Tolyllithium showed reactivity comparable to that of phenyllithium in p-$CH_3C_6H_4Li$/CO/ketone or ester reactions. With benzophenone and methyl benzoate, only the aryllithium trapping products, $(C_6H_5)_2(p\text{-}CH_3C_6H_4)COH$ (80% yield) and p-$CH_3C_6H_4C(O)C_6H_5$ (95% yield), respectively, were formed. The more hindered methyl pivalate gave both acylation and arylation products: p-$CH_3C_6H_4C(O)C(O)CMe_3$ (11%) and p-$CH_3C_6H_4C(O)CMe_3$ (67%). Introduction of the methyl substituent into the ortho position, i.e., using *o*-tolyllithium rather than *p*-tolyllithium, did not result in major changes in the course of the reactions (Scheme II).

The more hindered (2,6-dimethylphenyl)lithium gave much better results. With all substrates except pivala-

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[1] Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W.-L.; Archer, C. M. *J. Org. Chem.* **1992**, *57*, 5620.

[2] Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W.-L.; Archer, C. M. *J. Org. Chem.* **1991**, *56*, 5768.

[3] (a) Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1984**, *25*, 2623. (b) Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1984**, *25*, 5251. (c) Seyferth, D.; Hui, R. C. *J. Org. Chem.* **1985**, *50*, 1985.

[4] Seyferth, D.; Hui, R. C. *Organometallics* **1984**, *3*, 327.

[5] Seyferth, D.; Weinstein, R. M. *J. Am. Chem. Soc.* **1982**, *104*, 5534.

[6] Wittig, G. *Angew. Chem.* **1940**, *53*, 241 (footnote 58).

[7] Jutzi, R.; Schröder, F.-W. *J. Organomet. Chem.* **1970**, *24*, 1.

[8] Trzupek, L. S.; Newirth, J. L.; Kelly, E. G.; Sbarbati, N. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1973**, *95*, 8118.

[9] Nudelman, N. S.; Vitale, A. A. *J. Org. Chem.* **1981**, *46*, 4626.

[10] Nudelman, N. S.; Outumuro, P. *J. Org. Chem.* **1982**, *47*, 4347.

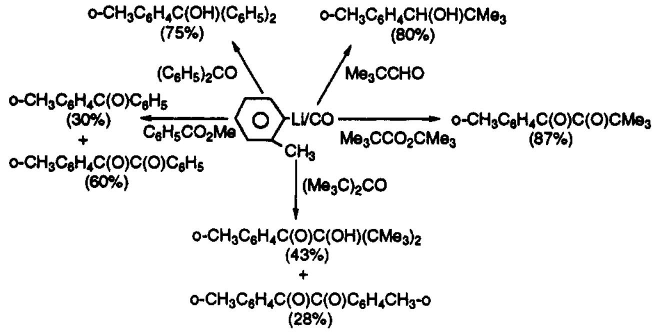
0022-3263/93/1958-5843$04.00/0

Table I. Reactions of ArLi, CO, and Various Electrophiles

Ar in ArLi (mmol)	electrophile (mmol)	product (yield, %)
C_6H_5 (8.35)	$(Me_2CH)_2CO$ (8.47)	$C_6H_5C(OH)(CHMe_2)_2$ (84)
C_6H_5 (7.74)	$(Me_3C)_2CO$ (7.75)	$C_6H_5C(O)C(OH)(CMe_3)_2$ (75)
C_6H_5 (9.0)	$(C_6H_5)_2CO$ (9.0)	$(C_6H_5)_3COH$ (80)
C_6H_5 (5.76)	$Me_3CCO_2CMe_3$ (5.82)	$C_6H_5C(O)C(O)CMe_3$ (45) + $C_6H_5C(O)C(O)C_6H_5$ (25)
C_6H_5 (9.0)	Me_3CCO_2Me (9.0)	$C_6H_5C(O)CMe_3$ (61) + $C_6H_5C(O)C(O)CMe_3$ (11)
C_6H_5 (9.0)	$C_6H_5CO_2Me$ (9.0)	$(C_6H_5)_2CO$ (94)
p-$CH_3C_6H_4$ (9.0)	$(C_6H_5)_2CO$ (9.0)	*p*-$CH_3C_6H_4C(OH)(C_6H_5)_2$ (80)
p-$CH_3C_6H_4$ (9.0)	Me_3CCO_2Me (9.0)	*p*-$CH_3C_6H_4C(O)CMe_3$ (67) + *p*-$CH_3C_6H_4C(O)C(O)CMe_3$ (11)
p-$CH_3C_6H_4$ (9.0)	$C_6H_5CO_2Me$ (9.0)	*p*-$CH_3C_6H_4C(O)C_6H_5$ (95)
o-$CH_3C_6H_4$ (9.24)	Me_3CCHO (9.18)	*o*-$CH_3C_6H_4CH(OH)CMe_3$ (80)
o-$CH_3C_6H_4$ (6.0)	$(Me_3C)_2CO$ (6.0)	*o*-$CH_3C_6H_4C(O)C(OH)(CMe_3)_2$ (43) + *o*-$CH_3C_6H_4C(O)C(O)C_6H_4CH_3$-*o* (28)
o-$CH_3C_6H_4$ (9.0)	$(C_6H_5)_2CO$ (9.0)	*o*-$CH_3C_6H_4C(OH)(C_6H_5)_2$ (75)
o-$CH_3C_6H_4$ (9.0)	$C_6H_5CO_2Me$ (9.0)	*o*-$CH_3C_6H_4C(O)C_6H_5$ (30) + *o*-$CH_3C_6H_4C(O)C(O)C_6H_5$ (60)
o-$CH_3C_6H_4$ (9.0)	$Me_3CCO_2CMe_3$ (9.0)	*o*-$CH_3C_6H_4C(O)C(O)CMe_3$ (87)
o-$CH_3C_6H_4$ (9.0)	$MeCO_2Me$ (9.0)	*o*-$CH_3C_6H_4C(O)Me$ (21) + *o*-$CH_3C_6H_4C(O)C(O)Me$ (10)
2,6-$(CH_3)_2C_6H_3$ (8.97)	Me_3CCHO (9.06)	2,6-$(CH_3)_2C_6H_3CH(OH)CMe_3$ (96)
2,6-$(CH_3)_2C_6H_3$ (9.0)	$(C_6H_5)_2CO$ (9.0)	2,6-$(CH_3)_2C_6H_3C(O)(C_6H_5)_2COH$ (90)
2,6-$(CH_3)_2C_6H_3$ (9.0)	Me_3CCO_2Me (9.0)	2,6-$(CH_3)_2C_6H_3C(O)C(O)CMe_3$ (96)
2,6-$(CH_3)_2C_6H_3$ (9.0)	$C_6H_5CO_2Me$ (9.0)	2,6-$(CH_3)_2C_6H_3C(O)C(O)C_6H_5$ (79)
2,6-$(CH_3)_2C_6H_3$ (9.24)	$EtMeCHCO_2Et$ (9.24)	2,6-$(CH_3)_2C_6H_3C(O)C(O)CHMeEt$ (79)[a] + *m*-xylene (17)[b]
2,6-$(CH_3)_2C_6H_3$ (10.1)	n-$PrCO_2Me$ (10.1)	2,6-$(CH_3)_2C_6H_3C(O)C(O)Pr$-*n* (50)[c] + *m*-xylene (29)[d]
2,6-$(CH_3)_2C_6H_3$ (9.0)[e]	$MeCO_2Me$ (9)	2,6-$(CH_3)_2C_6H_3C(O)C(O)Me$ (9) + *m*-xylene (48)
2,4,6-$(CH_3)_3C_6H_2$ (4.5)	$(C_6H_5)_2CO$ (4.5)	2,4,6-$(CH_3)_3C_6H_2C(O)C(OH)(C_6H_5)_2$ (15)
2,4,6-$(CH_3)_3C_6H_2$ (4.5)	$C_6H_5CO_2Me$ (4.5)	2,4,6-$(CH_3)_3C_6H_2C(O)C(O)C_6H_5$ (86)
2,4,6-$(CH_3)_3C_6H_2$ (4.5)	Me_3CCO_2Me (4.5)	2,4,6-$(CH_3)_3C_6H_2C(O)CMe_3$ (9) + 2,4,6-$(CH_3)_3C_6H_2C(O)C(O)CMe_3$ (35)

[a] 84% Yield in −135 °C reaction. [b] 13% Yield in −135 °C reaction. [c] 66% Yield in −135 °C reaction. [d] 20% Yield in −135 °C reaction. [e] Reaction at −135 °C.

Scheme II

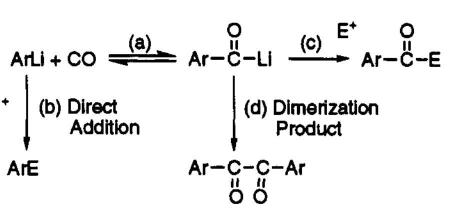


ldehyde, the acylation product was the only substrate-derived product (Table I), although variable quantities of *m*-xylene also were observed in some cases.

The results obtained when mesityllithium was used were less satisfactory, most likely as a result of the low solubility of this reagent in the solvent system used at −110 °C. In such reactions of this reagent the reaction mixture was white and milky at low temperature. Not until about −50 °C did the reaction mixture become clear. If mesityllithium does not react until it becomes soluble at higher temperature, then the occurrence of competitive and undesirable reactions is more likely. Changing the solvent system to 2:1 (by volume) THF/Me_2O did not improve matters. The *in situ* mesityllithium/CO/benzophenone reaction gave 2,4,6-$(CH_3)_3C_6H_2C(O)C(OH)(C_6H_5)_2$, but only in 15% yield. In the case of methyl pivalate, the acylation product, 2,4,6-$(CH_3)_3C_6H_2C(O)C(O)CMe_3$, was formed in 35% yield, but a 9% yield of 2,4,6-$(CH_3)_3C_6H_2C(O)CMe_3$ also was obtained. A noticeable improvement (50% yield of the α-diketone, only a 5% yield of the ketone, and a 30% yield of mesitylene) resulted when the reaction was carried out in pure THF at −100 °C. Methyl benzoate gave the best results at −110 °C, an 86% yield of 2,4,6-$(CH_3)_3C_6H_2C(O)C(O)C_6H_5$.

In conclusion, the results of this study have shown that direct, low temperature, *in situ* nucleophilic *aroylation* of organic carbonyl compounds is much less useful than direct nucleophilic *acylation*. Only when there is substantial steric hindrance to the addition of the aryllithium reagent to the ketone or ester does the chemistry shown in Scheme II occur. In the absence of such steric hindrance, addition of the aryllithium to the ketone or ester is favored. A possible explanation is that the ArLi + CO reaction (reported to be an electron-transfer process[11]) is slower than the alkyl-Li + CO reaction, so that, in the absence of steric hindrance, the ketone or ester can compete successfully with CO for the ArLi. A second possible explanation is that the carbonylation of organolithium reagents is a reversible process (Scheme III).

Scheme III



Thus the electrophile has an option to react with either the aryllithium or the aroyllithium. When both the electrophile and the aryllithium are unhindered, the direct addition reaction (b) is preferred. However, when either the electrophile or the aryllithium, or both, is bulky, reaction of the electrophile with aryllithium is hindered and reaction with the less-hindered aroyllithium is favored (reaction c). Thus the more hindered aryllithiums served well in the direct nucleophilic aroylation reaction. However, if the electrophile is very sterically hindered, e.g., *tert*-butyl pivalate, the reaction of the electrophile with the aroyllithium will also be hindered. In this case, dimerization of the aroyllithium also will occur. In the case of the alkyllithium/CO reaction, the equilibrium may be highly in favor of RC(O)Li. In any case, the direct, low

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(11) (a) Nudelman, N. S.; Doctorovich, F.; Amorín, G. *Tetrahedron Lett.* **1990**, *31*, 2533. (b) Doctorovich, F.; Nudelman, N. S.; Durán, R. XIX Congresso Latinamericano de Quimica, Buenos Aires, Nov 5–10, 1990, Abstract OR7.

temperature, *in situ* nucleophilic aroylation of organic electrophiles appear to be of rather limited applicability.

Experimental Section

General Comments. ***All reactions involving the use of CO were carried out in a good hood; CO is toxic, so due caution should be exercised.*** All glassware was flame-dried prior to use under a stream of prepurified nitrogen. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl, and pentane was distilled from lithium aluminum hydride prior to use. Dimethyl ether (Matheson) was passed through a drying tower of Drierite and condensed directly into the reaction flask. Carbon monoxide (Matheson) was used directly as received. Phenyllithium, *o*-tolyllithium, *p*-tolyllithium, and (2,6-dimethylphenyl)lithium were prepared by refluxing a mixture of lithium wire and the corresponding aryl bromides in ether according to the method of Rosenberg[12] and mesityllithium by refluxing a mixture of finely sliced lithium wire and 2-bromomesitylene in ether for 48 h, with good stirring. Addition of aryllithium solutions was effected with a syringe pump (Orion Research, Inc., Model 341 A). Melting points were uncorrected.

Total-immersion-type, low-temperature pentane thermometers (Kesler) were used to measure the temperature in the partial immersion mode. The readings usually are 7–8 °C higher compared to the actual temperature under our reaction conditions. The temperatures reported here all are corrected by subtracting 7 °C from the thermometer readings.

Analytical gas chromatography was carried out using a Perkin-Elmer 5754 Research chromatograph equipped with a 6 ft × $^1/_4$ in. 15% SE-30 on Chromosorb P column and a Gow Mac 550P Model chromatograph with a similar column. The program used for the separation of the compounds was 100–275 °C, heating at 6 °C/min. Yields by GLC were obtained using the internal standard method (C_8–C_{12}). Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Reactions between Aryllithium Reagents, Carbon Monoxide, and Electrophiles. Essentially the same procedure was used in all reactions. Therefore only one such reaction is described below.

Details of all other reactions are summarized in Table I. The products were simple ones. The IR and ^{1}H NMR spectra and their C,H analyses (collected as supplementary material) were in agreement with indicated structures. If the products were known compounds, their properties (mp, if solid), refractive index, and spectra were compared with those in the literature. IR, ^{1}H NMR, and analytical data are given in the supplementary material.

Reaction between Phenyllithium, Carbon Monoxide, and Di-*tert*-butyl Ketone at −110 °C. A 500-mL three-necked flask equipped with a mechanical stirrer, a Claisen adapter (fitted with low temperature thermometer and a gas outlet tube), and a no-air stopper which held a gas dispersion tube (which was connected to a carbon monoxide cylinder) was charged with 130 mL each of dry THF and diethyl ether, 40 mL of pentane, and di-*tert*-butyl ketone (1.10 g, 7.75 mmol). This solution was cooled to −110 °C with the aid of a liquid nitrogen-filled Dewar flask, and carbon monoxide was bubbled in for 30 min. Then phenyllithium (0.87 N solution in diethyl ether, 8.90 mL, 7.74 mmol) was added at 0.55 mL/min by means of the syringe pump. After the addition had been completed, the reaction mixture was stirred at −110 °C for 2 h while the stream of CO was continued. The brown reaction mixture then was allowed to warm to room temperature during the course of 1 h while CO was continuously bubbled through the solution. The reaction mixture changed to orange when it was warmed to room temperature. After hydrolysis with 75 mL of saturated NH_4Cl solution, the aqueous layer was separated and washed twice with diethyl ether. The organic phases were combined, dried over anhydrous $MgSO_4$, and filtered. The solvents then were removed under reduced pressure (15–20 mmHg). The residue was analyzed by GLC, (6 ft × $^1/_4$ in. SE-30/Chromosorb P; 100 °C to 275 °C at 6 °C per min, decane internal standard). Only one product was obtained. It was recrystallized from pentane and was identified as PhC(O)C(OH)(*t*-Bu)$_2$. Yield: 1.44 g (75%); NMR (250 MHz, CCl_4) δ 0.99 (s, 9H, C*Me*$_3$), 1.03 (s, 9H, C*Me*$_3$), 2.60 (s, 1H, *OH*), 7.35 (m, 5H, Ph); IR (Nujol, cm^{-1}) 3550 br (OH), 2960 s, 2880 s, 1680 s (C═O), 1445 s, 1395 w, 1365 s, 1280 m, 1210 m, 1070 s, 1005 m, 860 m, 740 m, 730 s, 700 s. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 76.88; H, 9.71. For reactions carried out at −135 °C, a solvent system composed of 3 volumes of dimethyl ether and 1 volume of THF was used.

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Supplementary Material Available: Physical, spectroscopic (^{1}H NMR and IR), and analytical data for products of ArLi/CO/organic substrate reactions (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[12] Rosenberg, S. D. *J. Am. Chem. Soc.* **1954**, *76*, 4389.