CARBONATION OF *ortho-*, *meta-* AND *para-*TRIFLUOROMETHYLPHENYLLITHIUM COMPOUNDS

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Summary

The three isomeric trifluoromethylphenyllithium compounds were carbonated under different conditions and the resulting products, acids, ketones and alcohols were isolated. The metalation of trifluoromethylbenzene with n-C_4H_9Li/TMEDA is also described.
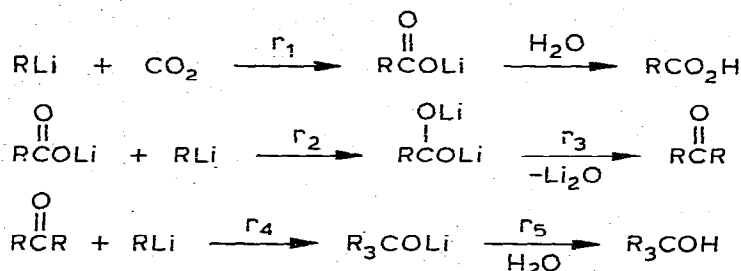
Introduction

Ortho, meta- and *para-*trifluoromethylphenyllithium compounds can be conveniently prepared through the metal—halogen exchange reaction of n-butyllithium and *o, m,* or *p*-bromotrifluoromethylbenzene [1], respectively. These organolithium compounds undergo a variety of reactions with a number of substrates. One of the more commonly reported reactions was carbonation of the organometallic to yield the trifluoromethyl substituted benzoic acid. Mixtures of *ortho, meta-* and *para-*trifluoromethylphenyllithium, from the direct metalation of $C_6H_5CF_3$ by n-C_4H_9Li, [2,3] have also been carbonated to yield mixed acids. In both instances, only acidic materials were reported without reference to any possible by-products. We are now reporting more detailed information on the synthesis, carbonation and resulting product analysis of the various reactions.

Results and discussion

A frequently reported reaction of an organolithium or organomagnesium compound is that of carbonation leading to the carboxylic acid derivative. In fact, isolation of an acid many times is used as proof of the existance of an organometallic precursor [4,5]. Although in many instances, good yields of acids have been obtained, detailed studies, especially in regards to rates of the various reactions possible during carbonation, have not been reported. Usually in carbonation studies, only the acid product is reported and only rarily is any by-product

formation mentioned. The reactions involved in carbonation of organolithium compounds have been postulated [6] to proceed according to the sequence shown in Scheme 1.

SCHEME 1

$$RLi + CO_2 \xrightarrow{r_1} \underset{\overset{\|}{O}}{RCOLi} \xrightarrow{H_2O} RCO_2H$$

$$\underset{\overset{\|}{O}}{RCOLi} + RLi \xrightarrow{r_2} \underset{\overset{|}{OLi}}{RCOLi} \xrightarrow[-Li_2O]{r_3} \underset{\overset{\|}{O}}{RCR}$$

$$\underset{\overset{\|}{O}}{RCR} + RLi \xrightarrow{r_4} R_3COLi \xrightarrow[H_2O]{r_5} R_3COH$$

Similar reactions have been postulated for the carbonation of Grignard reagents [7] whereby acids, ketones or alcohols may be produced in various yields depending on experimental conditions, structure and reactivity of the Grignard compound.

In our studies on the carbonation of o-, m- and p-trifluoromethylphenyllithium compounds (see experimental for details) we have found that the product distribution of the three isomers differs as indicated in Table 1. The *meta* and *para* isomers are quite different from the *ortho* isomer. One may speculate that the steric hindrance offered by the *ortho* CF_3 group may inhibit subsequent reaction of the o-$CF_3C_6H_4CO_2Li$ intermediate to yield the ketone and alcohol. The mode of carbonation is also important in governing product distribution. Without the benefit of a detailed study one can only speculate as to the reason for the various yields and product distribution. It seems plausible to suggest that the differences are due to the various rates of reactions $r_1 \rightarrow r_4$ which in turn are governed by a multiplicity of factors some of which may be, nucleophilic character of RLi, solvent, solubility of various intermediates, steric requirements, and mode of CO_2 addition.

A number of metalation studies of various aromatic compounds by C_4H_9Li have been reported [4]. Such studies were later extended to monosubstituted benzene compounds (RC_6H_5) with the objective of determining the directive

TABLE 1

CARBONATION PRODUCTS OF o-, m-, AND p-$CF_3C_6H_4LI$

Organolithium	% $CF_3C_6H_4CO_2H$[a]	%$(CF_3C_6H_4)_2$ C=O [a]	%$(CF_3C_6H_4)_3COH$[a]
o-$CF_3C_6H_4Li$	99.5 (I) [b]	<0.5 (II) [b]	0 [b]
m-$CF_3C_6H_4Li$	61 (III) [b] Trace (<1.0) [c]	25 (IV) [b] 78 [c]	14 (V) [b] 22 [c]
p-$CF_3C_6H_4Li$	64 (VI) [b] 0 [c] 43 [d]	30 (VII) [b] 89 [c] 50 [d]	6 (VIII) [b] 11 [c] 7 [d]

[a] Yields determined by GLC analysis. [b] RLi poured over crushed CO_2. A 62.2% yield for m-$CF_3C_6H_4CO_2H$ was previously reported [11] by this procedure, however no mention of ketone or alcohol formation was noted. [c] CO_2 gas bubbled into reaction mixture at 0°C. [d] CO_2 gas bubbled into reaction mixture at −78°C.

TABLE 2

PROPERTIES OF CARBONATION PRODUCTS OF o-, m-, and p-CF$_3$C$_6$H$_4$Li

Compound	M.p. ($^\circ$C)	Analysis Found (calcd.) (%)		Mol. wt. Found (calcd.)	IR (cm^{-1})
		C	H		
I	110	50.82	2.66	190	3010 (OH)
		(50.54)	(2.65)	(190)	1710 (C=O)
II	not isolated; identified by MS and GLC only				
III	106	50.75	2.54	190	3000 (OH)
		(50.54)	(2.65)	(190)	1690 (C=O)
IV	101	56.56	2.30	318	1660 (C=O)
		(56.61)	(2.53)	(318)	
V	viscous liquid	57.38	2.93	464	3610 (OH)
		(56.91)	(2.82)	(464)	
VI	224	50.52	2.19	190	3000 (OH)
		(50.54)	(2.65)	(190)	1700 (C=O)
VII	111	56.71	2.52	318	1655 (C=O)
		(56.61)	(2.53)	(318)	
VIII	90	56.73	2.52	464	3460 (OH)
		(56.91)	(2.82)	(464)	

effect of the substituent R towards metalation of the benzene ring. For example, CF$_3$C$_6$H$_5$ was metalated by C$_4$H$_9$Li [2,3]. The position and degree of metalation relative to the CF$_3$ group was established by carbonation of the reaction mixture and identifying the various isomeric acids. The yield of acids only were related to the degree of metalation which in turn was related to the directive influence of the CF$_3$ substituent. The total yield of mixed acids obtained was low, $\sim 33 \to 48\%$.

In view of our results (see Table 1) whereby variable yields of ketones and alcohols, in addition to the trifluoromethylbenzoic acids were obtained, caution must be exercised in interpreting studies whereby degree of metalation (or metal—halogen exchange [5]) is solely determined by acid content.

C$_4$H$_9$Li/TMEDA (1 : 1) complex has been reported [8] to metalate 1,3-bis-(trifluoromethyl)benzene exclusively in the 2 position in 30% yield. We have extended this metalation technique to C$_6$H$_5$CF$_3$ and have found that in addition to accelerating the rate of metalation under milder conditions, (see for comparison ref. [2 and 3]) much higher yields were possible and a more selective *ortho* metalation was observed. Under these conditions CF$_3$C$_6$H$_5$ was metalated to $\sim 95\%$. Carbonation of the reaction mixture and GLC analysis yielded the three isomeric acids and unreacted CF$_3$C$_6$H$_5$ (5%). Esterification of the acid mixture with diazomethane and GLC analysis of the mixed esters indicated the following product distribution: 96.5% *ortho*, 2.5% *meta* and 1.0% *para* substitution.

Experimental

General comments. All reactions were carried out in dried glassware under an atmosphere of dry, purified nitrogen. All melting points are uncorrected. Gas-liquid chromatography (GLC) (Hewlett—Packard Model 700) was used for yield determination. Isolated yields in all cases were slightly lower than GLC yields. All compounds prepared were analyzed by ^{19}F and ^{1}H NMR and results were

consistent with the structure. These data are not reported in this paper. Mass spectral analysis were performed on a DuPont Model 21-490 mass spectrometer. Infrared spectra were obtained using a Perkin—Elmer model 521 or 621 spectrophotometer as KBr wafer or neat liquids.

n-Butyllithium in hexane was purchased from Alfa/Ventron and was analyzed by the Gilman double titration method prior to use.

General procedure for carbonation of $CF_3C_6H_4Li$

A reaction flask containing p-$CF_3C_6H_4Br$ (22.5 g, 0.10 mole) dissolved in anhydrous diethyl ether (150 ml) was cooled to 0°C (ice bath). A hexane solution of n-C_4H_9Li (0.095 mol) was added over 8 min during which the colorless solution turned a deep amber and the reaction temperature rose to 6°C. After 30 min, a hydrolyzed (6 N HCl) sample was analyzed by GLC and indicated a trace of unreacted p-$CF_3C_6H_4Br$, and new peaks for $C_6H_5CF_3$ and C_4H_9Br. After 1 h, the reaction mixture was rapidly poured over freshly crushed CO_2. After warming to room temperature, the mixture was hydrolyzed (6 N HCl), phase separated and the aqueous layer further extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and analyzed by GLC indicating the following: p-$BrC_6H_4CF_3$ (trace), p-$CF_3C_6H_4CO_2H$ (64%), $(p$-$CF_3C_6H_4)_2$ CO (30%) and $(p$-$CF_3C_6H_4)_3COH$ (6%).

The entire reaction mixture was extracted with NaOH (0.25 N). The resulting basic layer was phase separated, acidified with HCl (conc.), extracted with diethyl ether and dried ($MgSO_4$). Aspiration of the solvent yielded p-$CF_3C_6H_4CO_2H$ (10.9 g, 62.3%). Recrystallization from hexane gave a pure acid, m.p. 228—229°C.

The non acid organic layer from above was dried ($MgSO_4$) and aspirated yielding 5.05 g of liquid—solid mixture. Filtration of the solid crystals yielded the ketone, $(p$-$CF_3C_6H_4)_2CO$ (3.70 g, 25.3%) which on recrystallization from petroleum ether (30—60°C) yielded a white crystalline solid, m.p. 114—116°C. The filtrate from above was placed on a silica gel column and eluted with a 50/50 petroleum ether (30—60°C)/benzene solution to yield the alcohol $(p$-$CF_3C_6H_4)_3$ COH (0.96 g, 6.7%). Recrystallization from petroleum ether (30—60°C) yielded a white solid, m.p. 93—95°C.

The m-$CF_3C_6H_4Li$ and o-$CF_3C_6H_4Li$ were carbonated similarly as described above.

With reverse carbonation (Table 1, note c, d), gaseous CO_2 was bubbled through the reaction mixture for 3.5 h and worked up as described above.

Metalation of $C_6H_5CF_3$

Into a reaction flask containing hexane (25 ml) and freshly distilled tetramethylethylenediamine (TMEDA) (11.6 g, 0.10 mol) was added a hexane solution of n-C_4H_9Li (0.10 mol). During the addition, the reaction was kept between 15—20°C by cooling with an ice bath. To this complex, $CF_3C_6H_5$ (14.6 g, 0.10 mol) was added in 5 min with cooling. After 3 h, Color Test II [9] for presence of n-C_4H_9Li was negative and Color Test I [10] for the presence of an aryllithium compound was positive. The reaction was carbonated by pouring rapidly over freshly crushed CO_2 and worked up as described above. GLC analysis prior to NaOH extraction indicated $CF_3C_6H_4CO_2H$ (95% mixed acids) and unreacted $CF_3C_6H_5$ (5%). After separation, 15.8 g of mixed acids $CF_3C_6H_4CO_2H$ (83%)

were isolated. The acids were esterifield by diazomethane and analyzed by GLC on a Dexsil column (2′, with a helium flow rate of 125 ml/min, isothermally at 100°C). Under these conditions, the three isomeric esters were separated and appeared as: *para*-7 min (1.0%); *meta*-8 min (2.5%) and *ortho*-9 min (96.5%).

References

1 A.E. Pavlath and A.J. Leffler, Aromatic Fluorine Compounds, Rheinhold Publishing Co., New York, 1962, and references cited therein.
2 J.D. Roberts and D.Y. Curtin, J. Amer. Chem. Soc., 68 (1946) 1658.
3 D.A. Shirley, J.R. Johnson, Jr. and J.P. Hendrix, J. Organometal. Chem., 11 (1968) 209.
4 H. Gilman and J.W. Morton Jr., Org. React., Vol. VIII, John Wiley and Sons, New York 1954.
5 R.G. Jones and H. Gilman, Org. React., Vol. VI, John Wiley and Sons, New York, 1951.
6 M.J. Jorgenson in W.G. Dauben (Ed.), Organic Reactions, J. Wiley and Sons New York, 1970, pp. 1—97.
7 M.S. Kharasch and O. Reinmuth, Grignard Reactions of Non-metallic Substances, Prentice—Hall, New York, 1954 p. 913.
8 D.E. Grocock and T.K. Jones, J. Chem. Soc. C, 3305 (1971).
9 H. Gilman and J. Swiss, J. Amer. Chem. Soc., 62 (1940) 1847.
10 H. Gilman and F. Schulze, J. Amer. Chem. Soc., 47 (1925) 2002.
11 H. Gilman and L.A. Woods, J. Amer. Chem. Soc., 66 (1944) 1981.