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Efficient methods for the preparation of acetylenic ketones

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Abstract

A number of acetylenic ketones $RC\equiv CC(=O)R'$ have been obtained in good yields from lithiated acetylenes $RC\equiv CLi$ and acetic anhydride, *N,N*-dimethylacetamide, or *N,N*-dimethylbenzamide. The most convenient and general method consists of treating alkynylzinc chlorides with acid halides $R'C(=O)Cl$. Benzoyl chloride ($R' = Ph$), acryloyl chloride ($R' = CH_2{=}CH$), and butynoyl chloride ($R' = C_2H_5C\equiv C$) react only in the presence of a catalytic amount of $Pd[P(Ph)_3]_4$.

Introduction

Acetylenic ketones can be prepared by acetylation of acetylenes as shown in the following general scheme [1–3].

$$RC\equiv C{-}M + R'C(=O)X \rightarrow \ldots \rightarrow RC\equiv CC(=O){-}R'$$

In this scheme X may be an alkali metal (mostly Li or Na), but other metal derivatives ($M = MgHal$, Cu, Ag, Cd, $Si\equiv$, $Sn\equiv$) have also been used. The acyl group has been introduced by reaction with an acid halide ($X =$ halogen), an acid anhydride ($X = OCOR'$), an acid amide ($X = NR''_2$), or a carboxylic ester ($X = OR''$).

Brown [1] and Yamaguchi [2,4] treated carboxylic anhydrides, *N,N*-dialkylcarboxylic amides and carboxylic esters with lithiated acetylenes in the presence of boron trifluoride etherate, which can activate the $C{=}O$ group for attack by the lithium alkynylide or enhance the leaving ability of the $OC(=O)R'$,NR''_2 or OR'' group. The Japanese workers used a large (100 mol% or more) excess of the lithiated acetylene.

In this paper we describe efficient procedures for the acylation of acetylenes that are suitable for preparation of sizable amounts of acetylenic ketones.

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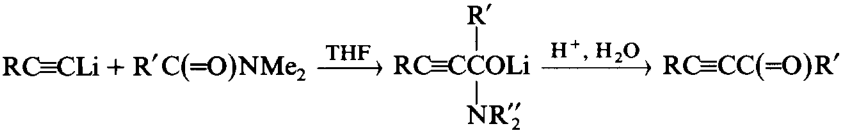
Results and discussion

a. Reaction of lithiated acetylenes with acetic anhydride

Addition at ~ −60 °C of an ethereal solution of the lithiated acetylene to a mixture of a 100 mol% excess of acetic anhydride and diethyl ether gave rise to a smooth reaction. The results obtained with three different types of acetylenes (see Table 1 and experimental part) suggest that this method can be applied to synthesize a number of acetylenic methyl ketones. It should be emphasized that it is not necessary to use $BF_3 \cdot Et_2O$ (cf. ref. 1). The excess of acetic anhydride can be removed by stirring the reaction mixture with aqueous sodium hydrogen carbonate or (more quickly) with dilute aqueous ammonia. Under these conditions no addition of NH_3 to the $C{\equiv}CC(=O)$ system occurs. We have not investigated whether use of a smaller excess of acetic anhydride would affect the results.

b. Reaction of lithiated acetylenes with N,N-dialkylcarboxamides

N,N-Dimethylacetamide is a cheap, commercially available compound, while the acid amides $t\text{-}C_4H_9C(=O)NMe_2$ and $PhC(=O)NMe_2$ are readily preparable from the commercially available acid chlorides. For these reasons, we have investigated the possibility of introducing $C(=O)Me$, $C(=O)t\text{-}C_4H_9$, and $C(=O)Ph$ groups by treating lithiated acetylenes with the carboxamides. Since the NR''_2 group is not eliminated from the adduct under the usual reaction conditions, the reaction mixture has to be treated with aqueous mineral acid.



$$RC{\equiv}CLi + R'C(=O)NMe_2 \xrightarrow{THF} RC{\equiv}C\underset{NR''_2}{\overset{R'}{C}}OLi \xrightarrow{H^+,\, H_2O} RC{\equiv}CC(=O)R'$$

As shown in Table 2, this reaction is suitable for the ketones in which R is either a saturated group or contains a double bond conjugated with the acetylenic function. The reaction of (equimolar amounts) $PhC{\equiv}CLi$ and $CH_3C(=O)NMe_2$ did not proceed to completion (ca. 40% of $PhC{\equiv}CH$ was recovered), and in the case of $CH_3C{\equiv}CC{\equiv}CLi$ the yield of the desired ketone was very low. It seems that the reaction reaches an equilibrium, which only lies on the side of the products when the lithiated acetylene is a sufficiently strong base. The same problem was encountered in the reactions of $C_3H_7C(=O)NMe_2$ with $C_2H_5C{\equiv}CLi$ and $C_2H_5C{\equiv}CC(=O)NMe_2$ (prepared from $C_2H_5C{\equiv}CLi$ and $ClC(=O)NMe_2$) with $C_2H_5C{\equiv}CLi$. With $t\text{-}C_4H_9C(=O)NMe_2$ no reaction at all was observed. Since we

Table 1

Acetylenic ketones $RC{\equiv}C\text{–}CO\text{–}CH_3$ from alkynyllithiums and acetic anhydride

R	B.p. (°C/mmHg)	n_D^{20}	Yield (%)	
$n\text{-}C_4H_9$	68/12	1.4462	60	
$CH_3CH{=}CH$	53–60/12	1.4951	57	*E*/*Z* ~ 60/40
$n\text{-}C_3H_7CH{=}CH$	~ 50/0.5	1.4760	63	only *Z*
$n\text{-}C_3H_7C{\equiv}C$	~ 60/0.5	1.5133	67	

Table 2

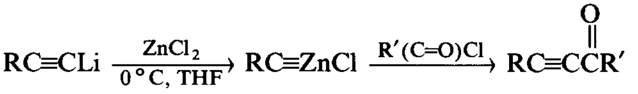
Acetylenic ketones $RC{\equiv}CCOR'$ from alkynyllithiums and *N*,*N*-dimethyl carboxamides $R'CONMe_2$

R	R′	B.p. (°C/mmHg)	n_D^{20}	Yield (%)
C_4H_9	CH_3	63/12	1.4482	88
cyclo-C_6H_9-1	CH_3	~ 50/0.5	1.5171	82
CH_3	Ph	~ 80/0.5	1.5447	80
$H_2C{=}C(CH_3)$	CH_3	46/15	1.4778	81

found a more generally applicable method for acetylenic ketones (see below) we made no attempts to improve the results with acid amides.

c. Reaction of alkynylzinc chloride with acid halides

Solutions of alkynylzinc chloride, readily made from alkynyllithium and an equivalent amount of anhydrous zinc chloride in tetrahydrofuran, reacted smoothly with the acid chlorides $CH_3C({=}O)Cl$ and $C_3H_7C({=}O)Cl$ at temperatures between 10 and 20 °C, while t-$C_4H_9C({=}O)Cl$ reacted at somewhat higher temperatures (40 to 50 °C). As shown in Table 3, a variety of acetylenic ketones was obtained in good to excellent yields. Our results contrast with the very low yield from the reaction of η-$C_6H_{13}C{\equiv}CZnCl$ with acetyl chloride reported by Negeshi et al. [5].



$$RC{\equiv}CLi \xrightarrow[0\,°C,\ THF]{ZnCl_2} RC{\equiv}ZnCl \xrightarrow{R'(C{=}O)Cl} RC{\equiv}C\overset{\overset{\displaystyle O}{\|}}{C}R'$$

Benzoyl chloride and the α,β-unsaturated acid halides $H_2C{=}CHC({=}O)Cl$ and $C_2H_5C{\equiv}CC({=}O)Cl$ did not react with alkynyllithium at 0–50 °C (compare also ref. 5). Prolonged interaction led to intractable products. This low reactivity may be attributed to resonance stabilization of the positive charge at the carbonyl carbon atom. In order to activate the C=O bond for the attack by the acetylide, we carried

Table 3

Acetylenic ketones $RC{\equiv}CCOR'$ from alkynylzinc chlorides and acid chlorides $R'COCl$

R	R′	B.p. (°C/mmHg)	n_D^{20}	Yield (%)	Notes
Ph	CH_3	~ 80/0.5	1.5720	78	[a]
Me_3Si	CH_3	50/15	1.4415	72	[a]
CH_3	C_3H_7	55/15	1.4447	87	[a]
Ph	C_4H_9	~ 90/0.5	1.5424	78	[a]
$H_2C{=}C(CH_3)$	CH_3	46/15	1.4759	67	[a]
$H_2C{=}CH$	C_3H_7	66/15	1.4722	66	[a]
$C_2H_5OCH(CH_3)OCH_2$	CH_3	~ 70/0.5	1.4456	65	[a]
$C_3H_7C{\equiv}C$	CH_3	~ 65/0.5	1.5130	70	[a]
C_2H_5	Ph	~ 90/0.5	1.5568	84	[b]
C_5H_{11}	$CH_2{=}CH$	~ 70/0.5	1.4710	68	[b]
Ph	$CH_2{=}CH$	~ 90/0.8	1.5928	56	[b]
C_2H_5	$C_2H_5C{\equiv}C$	~ 50/0.1	1.4894	47	[b]

[a] Without $Pd[P(Ph)_3]_4$. [b] With catalytic amount of $Pd[P(Ph)_3]_4$.

out the reactions in the presence of $Pd[P(Ph)_3]_4$. A small amount of $Pd[P(Ph)_3]_4$ (~ 0.2 to 0.5 mmol on a 0.1 molar scale) was sufficient to bring about a very smooth conversion: reactions on a 0.10 molar scale, with concentrations of reactants of the order of 0.5 to 0.8 mol/l were complete within 5 to 10 min at temperatures between 0 and 20 °C. Negeshi et al. [5] mention reaction times of "< 6 h" for their Pd^0-catalysed reactions. In the reactions with acryloyl chloride and butynoyl chloride, a relatively smooth subsequent reaction took place under the influence of the Pd^0-catalyst, resulting in the formation of undistillable viscous products. Reasonable (65–80%) yields of the ketones with the structure systems $C{\equiv}CC(=O)C{\equiv}C$ and $C{\equiv}CC(=O)C{=}C$ could be obtained by quickly adding (within 1 min) the acid chloride at −5 to +5 °C and hydrolysing the mixture within 10 min after the addition.

Concluding remarks

A number of acetylenic ketones can be prepared rather conveniently by reaction of lithiated acetylenes $RC{\equiv}CLi$ with acetic anhydride, *N*,*N*-dimethylacetamide or *N*,*N*-dimethylbenzamide, but the most versatile and convenient method seems to be acylation of alkynylzinc chloride with acyl halides, in some cases catalysed by $Pd[P(Ph)_3]_4$. The use of auxiliary reagents or catalysts is not necessary in the reactions of $RC{\equiv}CLi$ with acetic anhydride or of $RC{\equiv}ZnCl$ with saturated aliphatic acyl chlorides.

Experimental *

a. General procedure for the acylation of lithiated acetylenes with acetic anhydride (cf. ref. 3)

A solution of 0.10 mol of butyllithium in 70 ml of hexane was added dropwise during 15 min to a mixture of 0.11 mol of the acetylene and 90 ml of diethyl ether. During the addition, the temperature was maintained between −30 and −60 °C. The solution obtained was placed in a dropping funnel and added during 30 min to a mixture of 0.20 mol (100 mol% excess) of freshly distilled acetic anhydride and 100 ml of diethyl ether, maintained between −50 and −70 °C. After an additional 15 min 100 ml of a saturated aqueous solution of ammonium chloride was added with vigorous stirring and then a 10% aqueous solution of ammonia was added dropwise with vigorous stirring, with the temperature maintained between 10 and 20 °C. The addition was stopped when the pH reached 8. After separation of the layers, five extractions of the aqueous layer with diethyl ether were carried out. The combined organic solutions were washed with saturated aqueous ammonium chloride and subsequently dried over $MgSO_4$. The liquid remaining after removal of the solvent in vacuo was distilled; for further data see Table 1. Some ketones, especially those with a conjugated diyne system tend to polymerise during strong heating and so it is advisable to keep the bath temperature as low a possible during the distillation.

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* All compounds listed showed satisfactory purity (> 96%) according to GLC and NMR analysis.

b. General procedure for the acylation of lithiated acetylenes with N,N-dialkylcarboxamides

A solution of 0.10 mol of butyllithium in 70 ml of hexane was added dropwise during 15 min to a mixture of 0.11 mol of the acetylene and 90 ml of tetrahydrofuran with the temperature maintained between −30 and −60 °C. *N,N*-Dimethylacetamide or *N,N*-dimethylbenzamide (0.13 mol) was then added in one portion at ~ −30 °C. The mixture was warmed to 20 °C or in the case of dimethylbenzamide at 30 °C. After an additional half hour the solution was added during 2 min to a vigorously stirred mixture of 25 g of 37% aqueous hydrochloric acid and 200 ml of ice water. The pH of the aqueous phase was then adjusted to 6–7 by careful addition of concentrated aqueous K_2CO_3. The organic layer and four ethereal extracts of the aqueous layer were combined, washed twice with saturated aqueous ammonium chloride, and then dried over $MgSO_4$. Work-up was as described above. For further data see Table 2.

c. Reaction of alkynylzinc chloride with acyl chlorides (non-catalysed)

A solution of 0.10 mol of butyllithium in 70 ml of hexane was added dropwise during 15 min to a mixture of 0.11 mol of the acetylene and 50 ml of tetrahydrofuran with the temperature kept below −50 °C. Subsequently a solution of 0.10 mol of anhydrous zinc chloride in 50 ml of tetrahydrofuran was added during a few min at −20 to 0 °C. After an additional 10 min at 0 °C, 0.12 mol of freshly distilled acetyl, butyryl, or pivaloyl chloride was added in one portion at 5 °C. The temperature was allowed to rise to 25 °C (intermittent cooling was sometimes necessary in the case of acetyl and butyryl chloride) and kept there for 30 min. In the reaction with pivaloyl chloride, the mixture was kept at 45 °C for 30 min. The mixture was then added to 200 ml of an aqueous solution of 25 g of ammonium chloride. Concentrated aqueous ammonia (20 ml) was added, and the mixture was vigorously shaken. After separation of the layers, the aqueous layer was extracted with diethyl ether. The combined organic solutions were washed 5 times with small portions of saturated aqueous ammonium chloride and then dried over $MgSO_4$. Work-up was as described above. For additional data see Table 3.

d. $Pd[P(Ph)_3]_4$-catalysed reaction of alkynylzinc chloride with acryloyl chloride, butynoyl chloride and benzoyl chloride

A solution of 0.10 mol alkynylzinc chloride in 70 ml of hexane and 100 ml of THF was prepared as described in the previous experiment. $Pd[P(Ph)_3]_4$ (0.2 g in the cases of acryloyl chloride and benzoyl chloride, and 0.5 g in the case of butynoyl chloride) was introduced at 0 °C, followed by 0.11 mol of the acid chloride during 1 min at −5 °C (acryloyl chloride), +15 °C (benzoyl chloride) or 0 °C (butynoyl chloride). The temperature was allowed to rise to +10 °C (occasional cooling) or +25 °C (in the case of benzoyl chloride) and after an additional 10 min at the same temperature, 200 ml of pentane was added and the mixture then added to 200 ml of aqueous ammonium chloride. Work up was as described in exp. 3. For further data see Table 3.

e. Preparation of butynoyl chloride

Butynoic acid (0.20 mol, see ref. 3) and dichloromethane (20 ml) were placed in a 250 ml two-necked flask, equipped with a dropping funnel and a reflux condenser.

The mixture was warmed in a bath at ~ 80 ° C and freshly distilled thionyl chloride (0.20 mol) was added dropwise during 15 min with occasional swirling. The solution was then heated for an additional half hour under a stream of nitrogen. Subsequent careful distillation afforded butynoyl chloride, b.p. 36 ° C/15 mmHg, n_D^{20} 1.4670, in ~ 75% yield.

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