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A Straightforward Synthesis of Ynones by Reaction of Dimethylalkynylaluminum Reagents with Acid Chlorides

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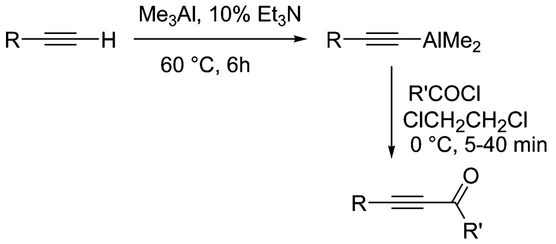

Alkynyldimethylaluminum reagents react with various aromatic and aliphatic acid chlorides in a fast and efficient way. This reaction provides a simple entry to numerous ynones, using readily available, inexpensive, and nontoxic metalating agent, and does not require any transition metal as a catalyst.

Ynones are extremely versatile substrates for further synthetic elaboration. α,β-Acetylenic carbonyl compounds can, for example, undergo sequential nucleophilic additions and cyclizations, leading in a simple and general manner to a full range of heterocyclic derivatives.[1] They can also serve as intermediates for the synthesis of natural products,[2] heterocyclic ligands, or precursors for materials with interesting properties.

As recently highlighted by Nájera and co-workers, a wide variety of synthetic approaches to conjugated acetylenic carbonyl compounds have been reported.[3] Among them, the palladium and/or copper-catalyzed cross-couplings of terminal acetylenic derivatives with acid chlorides are usually considered to be the methods of choice. Both approaches require the formation of the corresponding acetylides, either catalytically or stoichiometrically. In the case of the catalytic version, at least 1 equiv of a Brønsted base (generally a tertiary amine[4]) is, however, required to trap the acidic acetylenic proton, and the presence of this amine can lead to serious side reactions with some aliphatic acid chlorides or base-sensitive substrates.[5] This problem can be overcome using preformed metallic acetylides, but the presence of a palladium catalyst is still required to achieve clean and selective transformations.[6]

As a part of our work on the use of mixed dialkylalkynylaluminum reagents in stereoselective transformations,[7] we recently reported a straightforward access to these species by a base-catalyzed alumination of terminal alkynes (Figure 1)[8] and their palladium-catalyzed cross-coupling with aromatic halides.[9] We report here the reaction of such species with acid chlorides.

Although the coupling of aluminum acetylides with acid chlorides had been reported some years ago to require a catalytic amount of palladium,[10] the acylation of vinylalanes has been described to proceed without any catalyst.[11] Furthermore, ynones can classically be prepared starting from a silylated alkyne under Friedel−Crafts conditions in the presence of aluminum trichloride.[12] These results prompted us to reinvestigate the reaction of mixed dimethylalkynylalanes with acid chlorides.

First, experiments were conducted using heptynyldimethylaluminum and benzoyl chloride in THF. As expected, no ynone could be detected after 24 h, confirming that palladium catalysis is needed in this solvent. The use of DME led to the same results, whereas a complex mixture was obtained in toluene after 2 h at room temperature. However, we were pleased to find that a very fast reaction occurred in 1,2-dichloroethane, leading to the desired acylated compound (Table 1, entry 1). Best results were obtained when conducting the reaction at

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(3) Alonso, D. A.; Nájera, C.; Pacheco, Mª. C. *J. Org. Chem.* **2004**, *69*, 1615 and references cited.

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(5) The competitive formation of ketenes from aliphatic acid chlorides has been recently discussed: Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P. H.; Kantacha, A. *Chem. Commun.* **2005**, 1037.

(6) Direct acylations of acetylides have been reported: the use of alkali or alkaline-earth metals generally leads to complex reactions. The use of organocadmium reagents is hampered by the toxicity of Cd. Good results can be obtained with Cu or Mn acetylides, but the preparation of such reactive species generally requires transmetalation steps. For a general overview, see: (a) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177. See also: (b) Oh, C. H.; Reddy, V. R. *Tetrahedron Lett.* **2004**, *45*, 8545 and references cited in ref 3.

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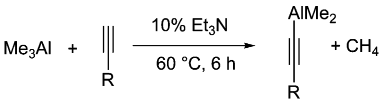
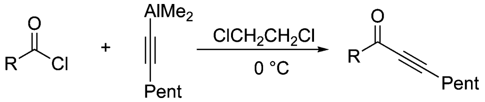


FIGURE 1. Triethylamine-catalyzed alumination of terminal alkynes.

TABLE 1. Reaction of Heptynyldimethylaluminum with Acid Chlorides



entry[a]	R	time (min)	yield (%)[b]
1	Ph	15	87
2	*p*-$MeOC_6H_4$-	10	87
3	*o*-$MeOC_6H_4$-	10	94
4	p-ClC_6H_4-	40	30[c]
5	thiophen-2-yl	20	86
6	Furyl-2-yl	120	no reaction[d]
7	$PhCH_2$	5	72
8	*n*-Pr	5	85
9	$CH_3(CH_2)_{13}CH_2$	5	82
10	*i*-Bu	5	91
11	*i*-Pr	5	88
12	cyclopropyl	10	98
13	*t*-Bu	10	86

[a] Reaction conditions: RCOCl (1 equiv), Pent-≡$AlMe_2$ (1 equiv). [b] Isolated yield. [c] A second addition of acetylide is observed as a side reaction. [d] A complex mixture is obtained after 24 h.

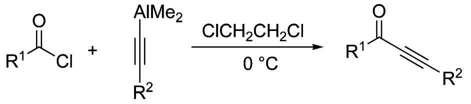
0 °C. At this temperature, methylene chloride and, to a lesser extent, toluene also proved to be suitable solvents for this reaction.

Various acid chlorides reacted in a very fast manner under these reaction conditions (Table 1). The reactivity of substituted benzoyl chlorides was generally good (entries 2 and 3) although the *para*-chloro derivative proved to be less reactive and led to a large amount of the corresponding alcohol as a result of longer reaction time and bis-alkynylation. A dramatic difference of reactivity could also be observed between thiophene- (entry 5) and furan- (entry 6) 2-carbonyl chlorides. More interestingly, acylation with aliphatic acid chlorides, bearing linear or branched, short or long alkyl chains, occurred in a very fast and clean manner, leading to the corresponding ynones in 72−98% yields (entries 7−13).

The coupling reaction was then investigated with various alkynes (Table 2). Phenylacetylene proved to be as reactive as heptyne in this acylation reaction, leading to ynones in less than 10 min and with yields between 88 and 97% (entries 1−3). Similar results could be obtained with a chlorinated acetylide (entries 4−6). Monoacylation of a monometalated terminal diyne could also be achieved, albeit in lower yields (entries 7−10). Although the palladium-catalyzed mono-cross-coupling with aromatic halides of such species has been reported to occur in a selective manner,[9] some bis-acylated products could be isolated from the crude reaction mixture.

The reaction of mixed alkynylalanes with oxalyl chloride is of particular interest. Although this reagent has been described to react with copper acetylides to deliver the corresponding acetylenic diketo derivatives,[13] the use of organoaluminum reagents led to the symmetrical diynone in 69% yield (Scheme 1). This decarbonylative process, typical for the behavior of oxalylchoride under Friedel−Crafts conditions,[14] enables a straightforward preparation of this useful intermediate.[15]

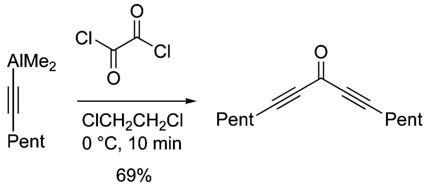
TABLE 2. Reaction of Alkynyldimethylalanes with Acid Chlorides



entry[a]	R^1	R^2	time (min)	yield (%)[b]
1	Ph	Ph	10	88
2	cyclopropyl	Ph	5	97
3	*i*-Bu	Ph	5	91
4	Ph	$ClCH_2(CH_2)_2$	10	88
5	cyclopropyl	$ClCH_2(CH_2)_2$	5	98
6	*i*-Bu	$ClCH_2(CH_2)_2$	5	90
7	Ph	$HC{\equiv}C(CH_2)_6$	10	42
8	p-$MeOC_6H_4$-	$HC{\equiv}C(CH_2)_6$	10	53[c]
9	cyclopropyl	$HC{\equiv}C(CH_2)_6$	5	60[c]
10	*n*-Pr	$HC{\equiv}C(CH_2)_6$	5	44

[a] Reaction conditions: R^1COCl (1 equiv), R_2-≡$AlMe_2$ (1 equiv). [b] Isolated yield. [c] Bis-acylation was the main side product (20% of bis-acylation for entry 8 and 19% for entry 9).

SCHEME 1. Synthesis of Symmetrical Diynone



In conclusion, the preparation of reactive acetylides using inexpensive, widely available, and nontoxic trimethylaluminum as a metal source via a triethylamine-catalyzed terminal metalation can provide a valuable alternative route to reactive acetylides in acylation reactions. This coupling reaction does not require any transition metal catalyst and occurs generally in less than 15 min at 0 °C, provided that the reaction is conducted in an appropriate solvent. This protocol enables the use of base-sensitive aliphatic acid chlorides, providing a general access to a wide range of ynones.

Experimental Section

The preparation of 1-phenyl-oct-2-yn-1-one (Table 1, entry 1) is representative. The alane solution was prepared according to the procedure described in ref 9. An argon-flushed Schlenk tube charged with acid chloride (0.5 mmol, 58 μL) and DCE (2 mL) was cooled to 0 °C with ice water, and the dimethylalkynylaluminum solution (1.0 equiv, 1.4 M in heptane, 0.36 mL) was then added dropwise. After the acid chloride disappeared (checked by TLC), an aqueous solution of Rochelle's salts[16] (2.0 M, 2 mL)

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was added to the vigorously stirred reaction mixture (caution: gas evolvement). Ether (5 mL) was added, and the organic phase was separated and washed with water and brine and dried over anhydrous Mg_2SO_4. Chromatographic purification on silica gel (eluent: cyclohexane/ethyl acetate 10/1) afforded 1-phenyl-oct-2-yn-1-one (87 mg, 87%).[17]

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Supporting Information Available: Analytical data for all new compounds and NMR spectra of every synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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