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An efficient dealkylative addition of trialkylamines to dialkyl acetylenedicarboxylates in the presence of a metallic chloride

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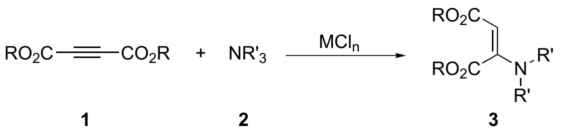
Abstract—Dialkyl acetylenedicarboxylates react effectively with an array of trialkylamines in dioxane at 80 °C in the presence of a metallic chloride to afford the corresponding aminomaleates in good yields.

The activation of unreactive bonds has been recognized as an attractive field in synthetic organic chemistry.[1] During the course of our studies directed towards ruthenium-catalyzed C–N bond activation of alkylamines, our group recently developed an alkyl group transfer from alkylamines to N-atom of anilines[2] as well as α-carbon atom of ketones[3] and an unusual reductive amination of aldehydes with tertiary amines.[4] In connection with this report, Winterfeldt reported that tertiary amino-esters and ketones reacted with methyl propiolate to afford β-aminocrotonates via a C–N bond cleavage of the starting amines.[5] It was also disclosed by Alaimo and Farnum that triethylamine was dealkylatively added to dimethyl acetylenedicarboxylate in the presence of a proton source to give aminomaleate.[6] Such a similar C–N bond cleavage was also exemplified by the reaction of dimethyl acetylenedicarboxylate with tertiary allylamines to give an 1:1 adduct via [3,3] rearrangement of allyl group from nitrogen to carbon of an initial zwitterionic intermediate formed from both substrates.[7] Under these circumstances, herein this report describes an efficient dealkylative addition of trialkylamines to dialkyl acetylenedicarboxylates in the presence of a metallic chloride.[8]

Table 1. Optimization of conditions for the reaction of **1a** with **2a**[a]

Entry	MCl_n	Solvents	Yield (%)
1	—	Dioxane	14
2	$LaCl_3$	Dioxane	42
3	$CeCl_3$	Dioxane	40
4	$SbCl_3$	Dioxane	76
5	$SnCl_2$	Dioxane	70
6	$SnCl_2$[b]	Dioxane	32
7[c]	$SnCl_2$	Dioxane	30
8	$SnCl_2$	Dioxane–H_2O[d]	27
9	$SnCl_2$	THF	46
10	$SnCl_2$	DMF	47
11	$SnCl_2$	Toluene	49

[a] Reaction conditions: **1a** (1 mmol), **2a** (5 mmol), MCl_n (1 mmol), solvent (10 mL), 80 °C, for 5 h.
[b] 0.1 mmol.
[c] At 25 °C.
[d] Dioxane (9.5 mL)–H_2O (0.5 mL).



Scheme 1.

The results of several attempted nucleophilic dealkylative additions of triethylamine (**2a**, **2**: R′ = Et) to dimethyl acetylenedicarboxylate (**1a**, **1**: R = Me) are listed in Table 1 (Scheme 1). Treatment of **1a** with 5 equiv of **2a** in dioxane at 80 °C afforded dimethyl 2-diethylamino-2-butenoate (**3a**, **3**: R = Me; R′ = Et) in only 14% yield (entry 1). However, when one equivalent of a metallic chloride was further added, the reaction rate was considerably enhanced towards aminomaleate formation (entries 2–5). Among the activity of various

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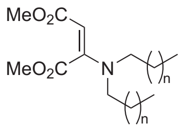
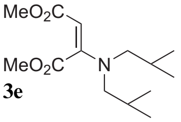
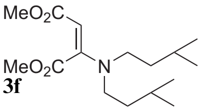
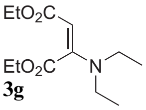
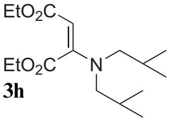
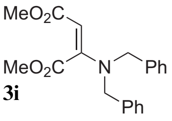
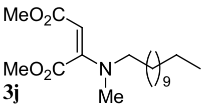
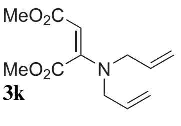
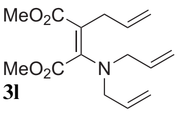
metallic chlorides examined antimony(III) chloride and tin(II) chloride revealed to be the additives of choice (entries 4 and 5). Equimolar amount of a metallic chloride relative to **1a** was required for the effective formation of **3a**. When the reaction was carried out in the presence of a catalytic amount (10 mol % to **1a**) of a metallic chloride, the addition did not occur effectively towards **3a** (entry 6). Performing the reaction at room temperature resulted in an unsatisfactory yield of **3a** (entry 7). Finally, among solvent examined, dioxane gave the best result and lower yield of **3a** was observed in the presence of water (entries 5 and 8–11).

Having established reaction conditions, various trialkylamines **2** were subjected to react with dialkyl acetylenedicarboxylates (**1a** and **1b**) in order to investigate the reaction scope and several representative results are summarized in Table 2. An array of trialkylamines (**2a**–**f**) having straight and branched alkyl chains reacted with **1a** and the corresponding aminomaleate

Table 2. Dealkylative addition of **2** to **1** leading to **3**[a]

1	Trialkylamines **2**	Products **3**	Yield (%)
$MeO_2C-\equiv-CO_2Me$			
1a	**2a** NEt_3	**3a** *n* = 0	76
1a	**2b** NPr_3	**3b** *n* = 1	74
1a	**2c** NBu_3	**3c** *n* = 2	70
1a	**2d** $N[(CH_2)_7CH_3]_3$	**3d** *n* = 3	70
1a	**2e** $N[(CH_2CH(CH_3)_2]_3$	 **3e**	76
1a	**2f** $N[(CH_2)_2(CH_3)_2]_3$	 **3f**	74
$EtO_2C-\equiv-CO_2Et$ **1b**	**2a**	 **3g**	83
1b	**2e**	 **3h**	62
1a	**2g** $N(CH_2Ph)_3$	 **3i**	0
1a	**2h** $Me_2N(CH_2)_{11}CH_3$	 **3j**	90
1a	**2i** $N(CH_2CH{=}CH_2)_3$	 **3k**	15
		 **3l**	33

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[a] Reaction conditions: **1** (1 mmol), **2** (5 mmol), $SbCl_3$ (1 mmol), dioxane (10 mL), 80 °C, for 5 h.

(**3a**–**f**) were obtained in similar yields irrespective of the alkyl chain length and bulkiness on **2a**–**f**. The reaction proceeds likewise with diethyl acetylenedicarboxylate (**1b**) to afford the corresponding aminomaleates in good yields. However, in the case of tribenzylamine (**2g**) the reaction did not proceed at all towards aminomaleate formation and the startings were recovered almost completely. The reaction of **1a** with *N*,*N*-dimethyldodecylamine (**2h**) gave dodecylmethylamino substituted maleate **3j** exclusively in preference to dimethylamino substituted maleate. Treatment of **1a** with triallylamine (**2i**) under the employed conditions preferentially afforded 1:1 adduct **3l** (33% yield) with concomitant formation of usual aminomaleate **3k** (15% yield). It is known that the former was produced via [3,3] rearrangement of allyl group from nitrogen to carbon of a zwitterionic adduct formed by the addition of **2i** to **1a**.[7] On the other hand, similar treatment of **2a** with ethyl 2-butynoate under the employed conditions gave no adducts.

General experimental procedure: a mixture of dialkyl acetylenedicarboxylate (1 mmol), trialkylamine (5 mmol) and antimony(III) chloride (1 mmol) in dioxane (10 mL) was placed in 25 mL round bottom flask and allowed to react at 80 °C for 5 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–chloroform) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give aminomaleates **3**.

In summary, it has been shown that antimony(III) chloride or tin(II) chloride catalyzes the dealkylative addition of trialkylamines to dialkyl acetylenedicarboxylates under the absence of proton source to give the corresponding aminomaleates in good yields. The exact reaction mechanism and synthetic applications are currently under investigation.

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