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A new method using 2-chloro-4,6-dimethoxy-1,3,5-triazine for facile elimination of dimethylamino group in Eschenmoser's methylenation for synthesis of α,β-unsaturated esters

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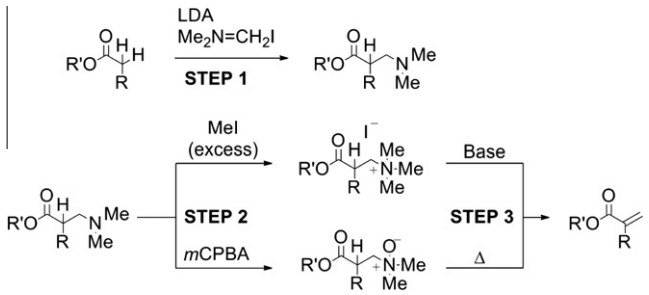
ABSTRACT

A facile one-step method for the elimination of the dimethylamino group in Eschenmoser's methylenation has been developed using a combination of 2-chloro-4,6-dimethoxy-1,3,5-triazine and triethylamine. The chemoselective elimination of the dimethylamino group occurred in compounds possessing either a diethylamino group or an alkylsulfanyl group.

Introduction

Methylenation at the α-position of a carbonyl group is a useful reaction in organic synthesis as the resulting α,β-unsaturated carbonyl groups occur in many natural products and are versatile functional groups that can undergo further transformation. Eschenmoser's methylenation is a reliable and widely used method for the introduction of a methylene group at the α-position of a carbonyl group.[1,2] However, this is a three-step reaction that can be both complicated and time consuming (Scheme 1). These steps include the introduction of an *N*,*N*-dimethylaminomethyl group using a base and *N*,*N*-dimethylmethyleneiminium iodide (Eschenmoser's salt) (STEP 1), conversion of the dimethylamino group to a trimethylammonio group by excess iodomethane (MeI)[3] (reaction time of approximately 24 h) or to an N-oxide (reaction time of approximately 10 min) using an oxidant such as *m*-chloroperbenzoic acid[4] (STEP 2), elimination of the trimethylammonio group by a strong base such as DBU, or that of N-oxide by thermolysis (STEP 3).

Developing a method for the rapid conversion of a dimethylamino group to a more reactive leaving group and enabling its subsequent facile elimination would allow chemists to conduct Eschenmoser's methylenation with both ease and efficiency. For this purpose, we chose 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) as a reagent for the activation of the dimethylamino group. CDMT is known to react with tertiary amines such as 4-methylmorpholine and *N*,*N*-dimethylglycine esters to form triazinylammonium salts that act as dehydrocondensing reagents such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM).[5] As these reactions complete within 30 min at room temperature,[6] the reaction of a dimethylamino group with CDMT is expected to proceed rapidly. In addition, the elimination of the resulting triazinylammonio group is expected to be faster than that of the trimethylammonio group because of the strong electron-withdrawing nature of the triazinyl group.[7] We have previously reported that when DMT-MM is suspended in CH_2Cl_2 for 3 h at room temperature, DMT-MM completely



Scheme 1. Traditional Eschenmoser's methylenation methods.

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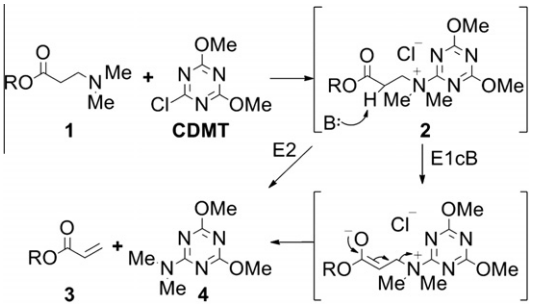
decomposes (96%) into 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)morpholine (DMTM) by demethylation because of the high leaving ability of DMTM.[8] In this study, we report a facile method for the elimination of a dimethylamino group in Eschenmoser's methylenation using CDMT.

Results and discussion

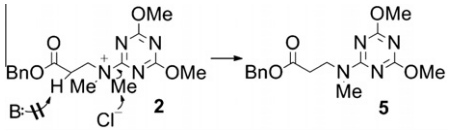
The reaction scheme that we have designed is illustrated in Scheme 2. When a β-dimethylamino ester **1** is treated with CDMT, the nucleophilic attack of the dimethylamino group proceeds to form the triazinylammonium salt **2**. Subsequent E2 or E1cB elimination of the resulting triazinylammonium salt **2** takes place to give the desired α,β-unsaturated ester **3** along with the formation of co-product **4**.

As expected, the reaction of benzyl 3-(dimethylamino)propionate (**1a**) using CDMT and triethylamine (Et_3N) as a base in CH_2Cl_2 at room temperature for 15 min afforded benzyl acrylate (**3a**) in 84% yield, along with a formation of 77% yield of co-product **4** (Table 1, entry 1).[9] The highest yield (94%) of **3a** was achieved when DMF was used as a solvent (entry 2). The reaction in MeCN and 2-PrOH also gave good yields (entries 3 and 4), whereas those in MeOH and THF gave somewhat lower yields (75% (entry 5) and 74% (entry 6), respectively). Because the yields of **4** did not decrease in the latter cases, the decomposition of **3a** by the 1,4-addition and/or polymerization due to its high reactivity might be responsible for decreasing its yields. Next, we examined the effect of changing the base in the reaction using DMF as a solvent. When the reaction was conducted with DBU, the yield of **3a** decreased (80%, entry 7). The reaction with K_2CO_3 and 4-methylmorpholine afforded only moderate yields (53% (entry 8) and 55% (entry 9), respectively). The reaction with pyridine or without the addition of any bases resulted in poor yields and the other by-product **5** was obtained (entries 10 and 11). The by-product **5** might be generated via a S_N2 reaction of the chloride anion with a methyl group attached to the nitrogen atom. Since deprotonation at the α-position of the carbonyl group hardly proceeded under neutral or weakly basic conditions, an alternative competing demethylation occurred in these cases (Scheme 3).

The effect of changing the chemical structure of the starting compound on the reaction was examined (Table 2). When the reaction was conducted in DMF with compound **1b**, which possesses a methyl group at the α-position, the yield decreased (50%) owing to competitive demethylation, which is probably because of the steric hindrance of the α-proton of the carbonyl group (entry 1). To avoid this demethylation, we used 2-PrOH instead of DMF to decrease the nucleophilicity of the chloride anion by solvation. As expected, the demethylation was prevented and the yield was increased to 90% (entry 2). A lactone type compound **1c** was converted into product **3c** in 77% yield (entry 3). Application to the compound **1d**, which possesses an ethylsulfanyl group that is susceptible to decomposition by electrophiles and oxidants, afforded **3d** in 86% yield (entry 4), whereas the reaction of **1d** with MeI (1 equiv)

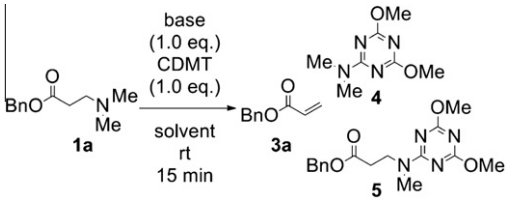


Scheme 2. Reaction scheme for the elimination of the dimethylamino group using CDMT and a base.



Scheme 3. Formation of by-product **5** from intermediate **2**.

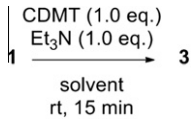
Table 1
List of solvent and base conditions

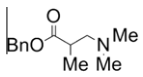
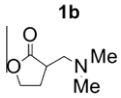
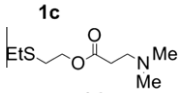
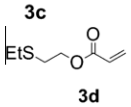
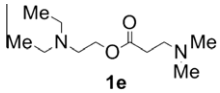
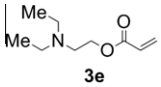


Entry	Solvent	Base	**3a**[a] (%)	**4**[a] (%)	**5** (%)
1	CH_2Cl_2	Et_3N	84	77	—[b]
2	DMF	Et_3N	94	93	—[b]
3	MeCN	Et_3N	89	92	—[b]
4	2-PrOH	Et_3N	85	95	—[b]
5	MeOH	Et_3N	75	91	—[b]
6	THF	Et_3N	74	88	—[b]
7	DMF	DBU	80	61	—[b]
8	DMF	K_2CO_3	53	70	—[b]
9	DMF	4-Methylmorpholine	55	71	—[b]
10	DMF	Pyridine	15[c]	16[c]	19[c]
11	DMF	None	15[c]	16[c]	15[c]

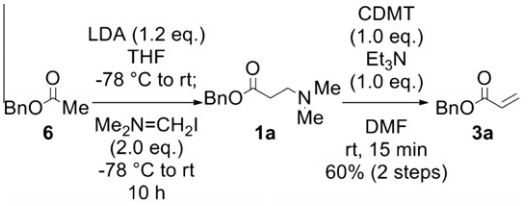
[a] Isolated yields.
[b] Not detected.
[c] Determined by ^1H NMR.

Table 2
Elimination of the dimethylamino group by CDMT and Et_3N



Entry	**1**	**3**	Solvent	Yield[a] (%)
1	 **1b**	 **3b**	DMF	50
2			2-PrOH	90
3	 **1c**	 **3c**	2-PrOH	77[b]
4	 **1d**	 **3d**	DMF	86
5	 **1e**	 **3e**	CH_2Cl_2	93

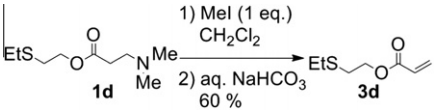
[a] Isolated yields.
[b] Because it was difficult to isolate **3c** from **4**, the yield of **3c** was estimated by ^1H NMR spectroscopy from a mixture of **3c** and **4** after column chromatography.



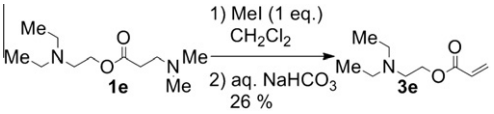
Scheme 4. Eschenmoser's methylenation using CDMT and Et_3N.

followed by elimination with aq $NaHCO_3$ gives **3d** in only 60% yield (Eq. 1). The reaction of **1e** possessing a diethylamino group proceeded via chemoselective quaternization of a dimethylamino group to give desired acrylate **3e** in 93% yield (entry 5),[10] whereas the reaction of **1e** with MeI (1 equiv) followed by elimination with aq $NaHCO_3$ affords **3e** in only 26% yield (Eq. 2). We reported that at least one methyl group is essential for the formation of triazinylammonium salts in acyclic tertiary amines because a β-alkyl group maintained in a gauche relationship with the nitrogen lone pair hinders the approach of CDMT to nitrogen (the gauche β-alkyl group effect).[11] Therefore, the observed high chemoselectivity between the dimethylamino group and the diethylamino group is attributed to the lower reactivity of the diethylamino group to CDMT by the *gauche* repulsion.[12]

Finally, we introduced a methylene group into benzyl acetate (**6**) using the Mannich reaction and demonstrated its subsequent elimination by CDMT and Et_3N (Scheme 4). The introduction of the dimethylaminomethyl group with lithium diisopropylamide (LDA) and Eschenmoser's salt followed by the elimination of the dimethylamino group by CDMT and Et_3N afforded **3a** in 60% over all yield:



(1)



(2)

In summary, we have demonstrated the use of a new method (the combination of CDMT and Et_3N) for the elimination of the dimethylamino group in Eschenmoser's methylenation. The elimination of the dimethylamino group afforded the corresponding α,β-unsaturated esters in good yields in one step and with short reaction times (15 min). This new method could also be applied to the compounds possessing a *N*,*N*-dialkylamino group with ethyl or larger alkyl substituents at the nitrogen atom, a structure to which conventional organic synthetic methods are unsuitable.[13]

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.092.

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6. Actually the reaction should be much faster because we can see a formation of the precipitate of DMT-MM within a couple of minutes.
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9. *General procedure for elimination reaction*: To a solution of benzyl 3-(dimethylamino)propionate **1a** (383 mg, 1.85 mmol) in DMF (9 mL) were added CDMT (325 mg, 1.85 mmol) and Et_3N (260 μL, 1.85 mmol) at room temperature. After being stirred for 15 min, the reaction mixture was partitioned between Et_2O and brine. The aqueous phase was extracted with Et_2O three times and the combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane:ethyl acetate = 15:1) to give benzyl acrylate **3a** (281 mg, 94%) as a colorless oil.
10. Because the reaction could not be worked up with water due to high polarity of **3e**, CH_2Cl_2 was used as a solvent. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was directly purified by flash column chromatography.
11. Kunishima, M.; Ujigawa, T.; Nagaoka, Y.; Kawachi, C.; Hioki, K.; Shiro, M. *Chem. Eur. J.* **2012**, *18*, 15856–15867.
12. For the same reason, Et_3N can work as a base without reacting with CDMT.
13. To the best of our knowledge, there is no example of application of traditional methods to the compounds possessing dialkylamino group.