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[3+2] Cycloaddition-mediated synthesis of 3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester

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ABSTRACT

1,3-Dipolar cycloaddition reactions are fundamental processes in organic chemistry. Herein we report [3+2] annulation of thiomethylacrylate **2** and azomethine ylide precursor **3** towards the synthesis of novel 3-methylsulfanyl-pyrrolidine **5**. Alternatively, we have also explored the alkylation of **7** with dimethyldisulfide/LDA for the introduction of thiomethyl group towards the synthesis of **5** in moderate to good yields. Efficacy of these two routes under various conditions/catalysts for the synthesis of **5** is presented.

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1,3-Dipolar cycloaddition reactions are fundamental processes in organic chemistry and offer an efficient and reliable synthetic methodology to access five-membered heterocycles, an important building block that forms the basic frame work of many natural products and pharmaceuticals.[1] In the last two decades, extensive studies have been performed in the area of [3+2] cycloaddition of azomethine ylides to synthesize highly substituted pyrrolidine moieties of their choice.[2]

[3+2] cycloaddition reactions which are usually carried out using Lewis and Bronsted acids such as anhydrous $AlCl_3$, $ZnCl_2$, $BF_3{\cdot}OEt_2$, $SnCl_4$ and TFA are among the most important reactions in organic chemistry as they lead to C–C bond formation. It is now well accepted that different types of clays such as Montmorillonite K-10, bentonite and zeolite can catalyze various organic transformations in an eco-friendly way. The Lewis acid properties of Montmorillonite K-10 have been successfully utilized for many other synthetic transformations.[3]

In this Letter we wish to report the synthetic application of [3+2] cycloaddition to synthesize 3-methylsulfanyl-pyrrolidine **5** catalyzed by Montmorillonite K-10 (Scheme 1).

Methyl 2-methylthioacrylate **1** was prepared quantitatively by chlorination of methyl 2-methylthiopropionates with sulfuryl chloride at 0 °C followed by dehydrochlorination using refluxing chloroform.[4] The acrylate **1** was reacted with azomethine ylide precursor **3** to give a smooth [3+2] annulation product 3-methylsulfanyl-pyrrolidine **4** (Scheme 1).

Lewis and Bronsted acid additives to assist the formation of the [3+2] annulated product **4** were also surveyed, but upon all attempts the yield of **4** was found to be significantly lower after the same reaction time (Scheme 1, Table 1, entries 1–6).

This transformation was carried out with different catalysts. Remarkably it was observed that Montmorillonite K-10 (Mont K-10) as an additive resulted in a significant acceleration of the reaction to furnish the cycloadduct **4**[5] in better yield in the same reaction time. (Table 1, entry 7).

Efficacy of the catalyst and optimization of the reaction was challenged by increasing the amount of the Montmorillonite K-10 loading in the reaction, however, a slight decrease in the yield of the product **4** was observed after the same reaction time (Table 1, entries 8–10). We found that an increase in the temperature to 50 °C decreased the yield of the product **4** (Table 1, entry 11).

Debenzylation of 1-benzyl-3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **4** bearing thiomethyl group was not successful under Pd/C reductions conditions due to catalyst poisoning by the thiomethyl group. Debenzylation was finally accomplished by heating **4** at reflux in 1,2-dichloroethane with 1 equiv of 1-chloroethyl chloroformate[6] for one hour resulting in the formation of 3-methylsulfanyl-pyrrolidine **5**[7] in good yield (Scheme 1).

Alternatively, we have also explored the alkylation of **7** with dimethyldisulfide/LDA at −78 °C that led to the introduction of thiomethyl group to give **8** in moderate yield (Scheme 1). Deprotection of the BOC group was accomplished using TFA to give 3-methylsulfanyl-pyrrolidine **5** in good yield.

Both synthetic approaches allowed the introduction of the thiomethyl group at the 3-position of the pyrrolidine ring to give **5** and are compared in terms of reaction viability and yields. The overall yield of alkylation route, that is, **5** from **6** is comparable to the cycloaddition routes **1** to **5** (Scheme 1). For the multigram preparations of **5**, the cycloaddition approach is preferred over the alkylation method.

Montmorollonite K-10 catalyzed [3+2] cycloaddition-mediated synthesis of 3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **4** involves reaction conditions that are environmentally friendly, amenable for scale-up and simple to work-up.

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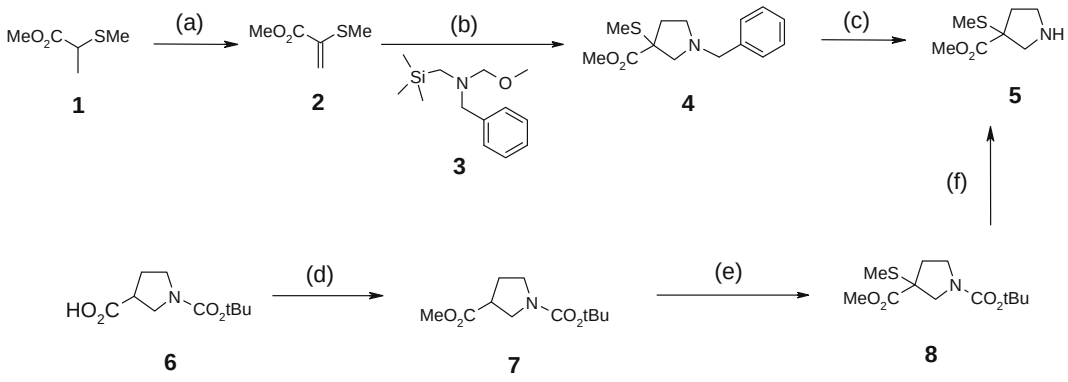

Scheme 1. Reagents and conditions: (a) SO_2Cl_2, $CHCl_3$, 100%; (b) catalyst, **3**, conditions (see, Table 1); (c) 1-chloroethyl chloroformate, proton sponge, CH_2Cl_2, 86%; (d) CH_2N_2, MeOH, 100%; (e) LDA, $(SMe)_2$, THF, −78 °C, 60%; (f) TFA, CH_2Cl_2, 90%.

Table 1
[3+2] cycloaddition-mediated synthesis of 1-benzyl-3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **4**

No.	Catalyst	Conditions	Yield (%)
1	$(Tf)_2NH$	rt, CH_2Cl_2, 72 h	13
2	TFA	0 °C to rt, CH_2Cl_2, 72 h	18
3	$InCl_3$	rt, CH_2Cl_2, 72 h	30
4	LiBF4	rt, CH_2Cl_2, 72 h	32
5	$BF_3{\cdot}Et_2O$	0 °C to rt, CH_2Cl_2	33
6	CSA	rt, CH_2Cl_2, 72 h	36
7	Mont. K-10	10% w/w, rt, CH_2Cl_2, 72 h	60
8	Mont. K-10	20% w/w, rt, CH_2Cl_2, 72 h	43
9	Mont. K-10	30% w/w, rt, CH_2Cl_2, 72 h	49
10	Mont. K-10	100% w/w, rt, CH_2Cl_2, 72 h	54
11	Mont. K-10	10% w/w, 50 °C, Cl CH_2CH_2Cl, 72 h	22

In summary, we have demonstrated Montmorollonite K-10 to be an efficient catalyst for the [3+2] cycloaddition-mediated synthesis of 3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **5**. Further studies on the potential synthetic applications of this novel 3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **5** in medicinal chemistry are underway and the results will be reported in due course.

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5. *General procedure for the [3+2] cycloaddition*: To a stirred solution of 2-ethoxyacrylate 2-methylsulfanyl-acrylic acid methyl ester **2** (136 g, 1.03 mol) and benzyl-methoxymethyl-trimethylsilanylmethyl-amine **3** (290 g, 1.22 mol) in dichloromethane (2.7 L) was added catalyst (see Table 1 for conditions). The resulting solution was warmed to room temperature and was stirred for 3 days. The crude product after filtration was purified by column chromatography on silica gel eluting with a solution of EtOAc/hexane(1:4) to give 1-benzyl-3-methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester **4**. ^{1}H NMR δ ($CDCl_3$) 7.30 (4H, d, *J* 4.2 Hz), 7.26–7.22 (1H, m, 3.9 Hz), 3.74 (3H, s), 3.67 (1H, d, *J* 13 Hz, 6.4 Hz), 3.63 (1H, d, *J* 13 Hz, 6.4 Hz), 3.34 (1H, d, *J* 10.2 Hz), 2.79–2.74 (1H, m), 2.70–2.58 (3H, m) 2.07 (3H, s), 2.01–1.96 (1H, m). ^{13}C NMR ($CDCl_3$) δ 173.1, 138.5, 128.5, 128.2, 127.0, 62.3, 59.7, 54.8, 52.8, 52.5, 34.7, 13.8. HRMS (ESI) calculated for $C_{14}H_{20}N_1O_2S$ $[M+H]^+$: 266.12147, found 266.12126.
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7. *3-Methylsulfanyl-pyrrolidine-3-carboxylic acid methyl ester* **5**: ^{1}H NMR δ ($CDCL_3$) 8.77 (1H, br s), 3.88 (1H, br s), 3.80 (3H, s), 3.63 (1H, br s), 3.56 (2H br s), 2.59 (2H, br s), 2.18 (3H, s). ^{13}C NMR ($CDCl_3$) δ 170.0, 55.0, 53.2, 51.0, 44.4, 33.3, 13.8 HRMS (ESI) calculated for $C_7H_{14}N_1O_2S$ $[M+H]^+$: 176.07452, found 176.0741.