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3,3-Dimethoxypropylsulfonyl Group: A new versatile protecting and activating group for amine synthesis

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ABSTRACT

3,3-Dimethoxypropylsulfonyl (Dimps) chloride was prepared and used as a new versatile sulfonating agent for ammonia, primary and secondary amines to afford corresponding Dimps-amides in excellent yields. The resulting *N*-nonsubstituted and *N*-monosubstituted Dimps-amides, activated amines, were alkylated satisfactorily under new Mitsunobu conditions. The Dimps group was removed by treatment in aqueous solution under acidic followed by basic conditions. Furthermore, epilachnene, the defensive droplets from the Mexican bean beetle, *Epilachna varivestis*, was synthesized utilizing this Dimps methodology in short steps.

1. Introduction

In the synthesis of nitrogen-containing molecules with a wide variety of interesting biological activities, protection and/or activation of the nitrogen atom followed by deprotection procedures are common processes in the construction of nitrogen functional groups. Thus, many protecting and/or activating groups have been developed and applied to various stages of organic syntheses.[1] Among them, the Fukuyama method utilizing the *o*-nitrobenzenesulfonyl (Ns) group has been widely accepted and applied to amine synthesis because of its sufficient stability toward various reagents and mild and easy conditions to remove the group.[2] Further, the *o*-anisylsulfonyl (Ans) group was developed as an alternative activating/protecting group of the nitrogen functionality.[3]

In the course of our studies on the Mitsunobu chemistry utilizing (cyanomethylene)tributylphosphorane (CMBP) and/or (cyanomethylene)trimethylphosphorane (CMMP),[4,5] we proposed the 2-(1,3-dioxan-2-yl)ethylsulfonyl (Dios) group (**1**) (Fig. 1) as a new versatile sulfonyl group for amino activation/protection and employed it for the preparation of a wide variety of primary and secondary amines.[5] To expand this chemistry, we recently designed 3,3-dimethoxypropylsulfonyl (Dimps) group (**3**), which could be removed more easily than the Dios group (**1**). Even so, the reactivity of Dimps-amides (**4**) activated amines under the Mitsunobu reaction conditions was expected to be similar to that of Dios-amides (**2**), because the pK_a values of both are estimated to be the same as that of aliphatic sulfonamides (e.g., MsNHMe: pK_a = 11.8).[6]

2. Results and discussion

Dimps chloride (**7**), a sulfonyl agent, was prepared by the following reaction sequence: 1) commercially available 3,3-dimethoxypropylchloride (**5**) was converted to the corresponding sodium 3,3-dimethoxypropylsulfonate (**6**) using Na_2SO_3 (DME-H_2O, 110 °C, 72 h in an Ace pressure tube with vigorous stirring), and then 2) the sulfonate **6** was treated with 2.0 equiv of PPh_3 and 2.2 equiv of sulfuryl chloride (CH_2Cl_2, −10 °C, 2 h). The agent **7** could be purified by rapid chromatography (*n*-hex./ether = 1/1) on silica gel and stored at −15 °C for at least one month (Scheme 1).

The reaction of **7** with ammonia afforded water-soluble *N*-nonsubstituted Dimps-amide (**8**) in 95% yield (NH_3 aqueous, CH_3CN, 0 °C to room temperature, 10 min). Primary and secondary amines were also sulfonated in excellent yields (1.1 equiv of **7**, 1.5

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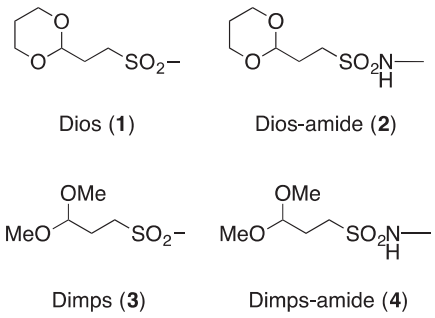
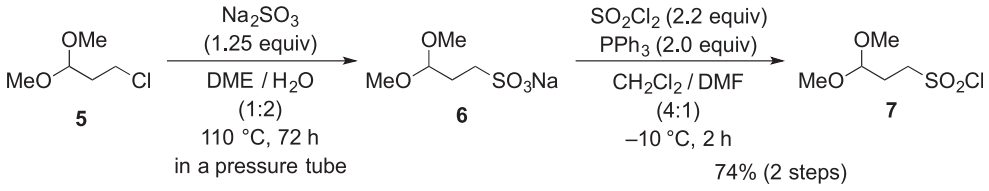


Fig. 1. Dios and Dimps groups.

and allylic alcohols gave overreacted product **10** (double alkylation products) to some extent because of their high reactivity.

As shown in Table 3, *N*-monosubstituted Dimps-amides (**9**) could also be subjected to the Mitsunobu alkylation utilizing CMMP[7] which possessed sufficient reactivity to afford *N*,*N*-disubstituted Dimps-amides (**10**) in excellent yields.

We reported previously that the Dios group (**1**) was cleaved by the treatment in hot 80% aqueous trifluoroacetic acid to afford primary and secondary amines in high yields.[5] However, the deprotection of substances with trisubstituted olefins such as the geranyl group failed to give desired amines even at room temperature and with less amounts of trifluoroacetic acid (50%) (e.g., Scheme 2).

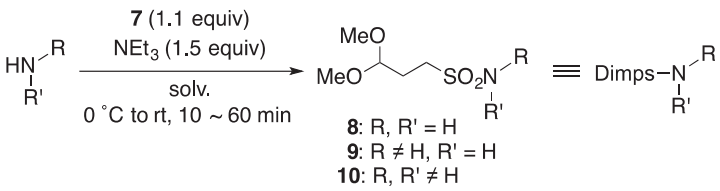


Scheme 1. Preparation of **7**.

equiv of NEt_3, CH_2Cl_2, 0 °C to room temperature, 10–30 min), as listed in Table 1.

The feature of the reaction of **8** in the presence of CMBP was quite similar to that of the Dios-amide reported previously.[5] Thus, the Mitsunobu alkylation of **8** proceeded in satisfactory yields to give **9** even with secondary alcohols (Table 2), even though benzylic

Table 1
Reaction of amines with **7**.



entry	amine	Solvent	Dimps-amide	Yield (%)
1	NH_3 aq.[a]	CH_3CN	Dimps–NH_2 **8**	95
2	Ph, NH_2	CH_2Cl_2	Dimps–N(H), Ph **9a**	99
3	NH_2	CH_2Cl_2	Dimps–N(H) **9b**	99
4	NH_2, Hex	CH_2Cl_2	Dimps–N(H), Hex **9c**	96
5	NH_2	CH_2Cl_2	Dimps–N(H) **9d**	84
6	HN, Ph	CH_2Cl_2	Dimps–N, Ph **10a**	84

[a] Reaction was carried out without NEt_3.

We expected that the Dimps group (**3**) could be removed more easily than **1**. Eventually, the deprotection of **3** was accomplished with a two-step operation in one pot as follows: 1) acid-catalyzed hydrolysis of the acetal moiety to the aldehyde in an aqueous acetone or acetonitrile solution of *p*-tolenesulfonic acid (*p*-TsOH) at room temperature, and then 2) basification with the addition of 1 M NaOH or solid K_2CO_3 with a small amount of water for a retro-Michael reaction,[8] giving the corresponding primary and secondary amines in high yields (Tables 4 and 5).[9] *N*-Monosubstituted Dimps-amides **9** could be cleaved more easily than *N*,*N*-disubstituted Dimps-amides **10**. Under these conditions, the geranyl group could survive satisfactorily. Furthermore, we confirmed that Dios-amide was sufficiently stable under these aqueous acidic conditions to recover itself (only 2% hydrolysis after 14 h). Otherwise, the Dimps group could also be cleaved by treatment with TMSOTf in good yield (Scheme 3).

We prepared compound **17**[10] bearing the Dimps group with *tert*-butoxycarbonyl (Boc) and Ns groups on nitrogen atoms and examined the selective deprotection of each group as follows (Scheme 4): 1) acid-catalyzed hydrolysis followed by basification cleaved the Dimps group to afford **18**, 2) treatment with thiophenol-K_2CO_3 cleaved the Ns group to give **19**, and 3) treatment with conc. H_2SO_4 in MeOH removed the Boc group quite significantly to yield **20**. Thus, the Dimps group can be utilized not only as an activating group but also as a new amine-protecting group. In conclusion, the order of the stability of Boc, Dios and Dimps group under aqueous acidic conditions[11] is Dios > Boc > Dimps.

To demonstrate the usefulness of the Dimps methodology, we synthesized epilachnene (**21**)[12] again. In the previous synthesis,[13] tosylamide **23** was employed as a nitrogen nucleophile under Mitsunobu conditions (CMMP) followed by lactonization to afford **25**, whose tosyl group was removed smoothly by reductive conditions using sodium naphthalenide at −40 °C in DME. However, the product of the reaction was undesired lactam **26** generated by intramolecular acyl migration. So, *trans*-lactonization of **26** was carried out by treatment with *p*-toluenesulfonic acid (Scheme 5).

This time, Dimps-amide **27**[10] was utilized to overcome this problem (Scheme 6). Alcohol **22**[14] was subjected to the Mitsunobu reaction with **27** in the presence of CMMP to yield Dimps-amide **28**, which was treated with base in hot aqueous ethanol to provide