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THE 3,4-DIMETHOXYBENZYL MOIETY AS A NEW N-PROTECTING GROUP OF 1,2-THIAZETIDINE 1,1-DIOXIDES.

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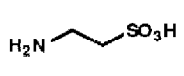
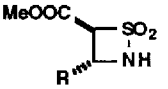
Abstract *The 3,4-dimethoxybenzyl group was used to N-protect 3,4-diphenyl 1,2-thiazetidine1,1-dioxide derivatives It is smoothly eliminated by 2,3-dichloro 5 6-dicyanobenzoquinone (DDQ), the yield depending on the substituents of the 3-phenyl ring*

Since several years, we have been interested in 1,2-thiazetidine 1,1-dioxides as synthetic intermediates for the preparation of biological active compounds [1] Our group and others have demonstrated the utility of these four-member heterocycles in the synthesis of taurine (an abundant free aminosulfonic acid found in mammals) analogues [2] and of β-lactam antibiotic analogues [3] , moreover these β-sultams have been only marginally studied [4, 5]



Taurine

1,2-Thiazetidine 1,1-Dioxide
β-Sultam



β-Sultam Antibiotics

Recently Szymonifka and coll developped the first N-protecting group of 1,2-thiazetidine 1 1-dioxides using the phenylselenylethyl moiety [3] This study prompted us to publish our own results in the same chemical area, and we describe here the synthesis of compounds 1, 2 and 3 (scheme 1)

As Szymonifka and coll did we also tried to apply usual N-protecting groups of β-lactams to β-sultams but we were unable to remove the 4-methoxyphenyl [6], 2,4-dimethoxybenzyl [7] and also benzyl [8] groups from the nitrogen atom of our thiazetidines In the literature [9], the 3,4-dimethoxybenzyl (3,4-DMB) O-protecting group is mentioned as being easier to eliminate than 4-methoxyphenyl We synthesized then the new N-3,4-DMB-protected 1,2-thiazetidine 1,1-dioxides 4, 5 and 6 (scheme 1) by the method described in ref 2 [10] The 3,4-DMB protecting group was smoothly removed by oxidation with 2,3-dichloro 5,6-dicyanobenzoquinone (DDQ) in 8 to 50% yield (table 1) [11] Other products present in the reaction mixture are only the 3,4-dimethoxybenzaldehyde formed during the oxidation and the initial N-protected thiazetidine which can be recovered and recycled

We observe that the yield of the deprotection decreases when the para-position of the 3-phenyl ring is substituted with an electron-withdrawing group (table 1) This result is totally in accordance with the well-established mechanism of DDQ oxidation [12]

Under alkylating conditions (NaH, CH_3I) we obtained compound 7 from 5 with honest yield for this type of reaction [5] On the other hand, treatment of 5 with HCl 6N or MeONa/MeOH resulted in the formation of molecule 8 by hydrolysis of the heterocyclic sulfonamide bond These three experiments, where the 3,4-DMB was not removed nor modified, illustrate the large usefulness of the 3,4-DMB group

This original thiazetidine N-protecting group (3,4-DMB) has the advantage to be easily and very rapidly introduced from commercial non toxic reagents and to be smoothly eliminated in only one step, in short contrast to the phenylselenylethyl group Moreover, the use of DDQ as reagent presents also several distinct advantages over methods previously described DDQ is commercially available, no specific equipments are required, both reaction and work-up are particularly easy and the by-product $DDQH_2$ can be recycled to the reagent by nitric oxidation [13]

SCHEME 1

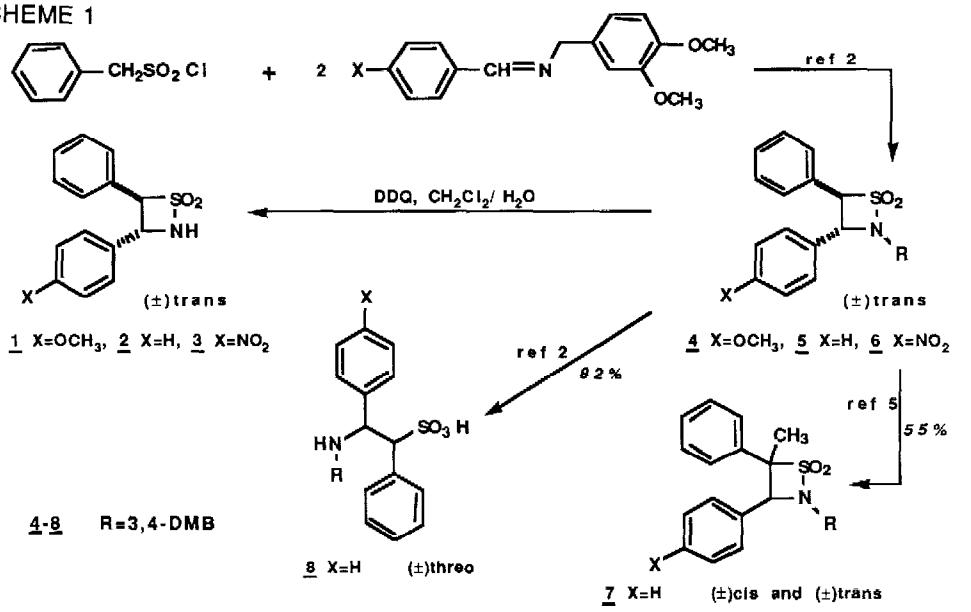


TABLE 1

Compound	X	DDQ eq	Yield (%) [a]
1	OCH_3	1 1	30
1 [14]	"	2 1	40
2 [14]	H	1 1	50
3 [14]	NO_2	1 1	8

[a] yields are reported for pure and isolated product

In conclusion, we demonstrate here that despite the relatively low deprotection yield obtained in the case of compound 6 (X=NO_2), the 3,4-DMB N-protecting group can be a useful tool in the particular chemistry of 1,2-thiazetidine 1,1-dioxides This result illustrates also the possibility of using the 3,4-DMB group alternatively to the phenylselenylethyl moiety

References and notes

1 This work forms a part of the PhD submitted by E Grunder-Klotz at the University of Louis Pasteur She was recipient of a Ministry of Research and Technology fellowship (MRT)
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10 All new compounds were fully characterized by their IR, ^1H NMR, ^{13}C NMR MS data and microanalysis
11 General procedure is as follows DDQ was rapidly added to a solution of thiazetidine substrate (10 mmol l^{-1}) in CH_2Cl_2/H_2O 20/1 Stirring was maintened for 12-24H at room temperature The precipitate of $DDQH_2$ formed is then filtered and the filtrate is evaporated under vacuum The crude products were purified by silica gel column chromatography (eluent Hex/CH_2Cl_2/Diethylether in variable concentrations)
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14 Compound 1 mp (Hex/AcOEt 75/25) 108°C IR ($CHCl_3$) $\overline{\nu}$ (SO_2) 1160-1320 and $\overline{\nu}$ (NH) 3320 cm^{-1} ^1H NMR ($CDCl_3$, 200MHz) δ 3 80 (s, 3H, OCH_3), 4 80 (m, 1H, CHN), 5 31 (d, 1H, CHS, J=7 0Hz) 5 74 (d, 1H, exchangeable with D_2O, NH, J=5 2Hz), 6 87-7 50 (m 9H**arom**) MS m/z (relative intensity) 289 (41, M^+), 225 (55, $[M-(SO_2)]^+$), 211 (53), 135 (100, $[NH{=}CHC_6H_4OCH_3]^+$) Anal Calcd for $C_{15}H_{15}NO_3S$ C 62 27, H, 5 23, N, 4 84 Found C, 62 21, H, 5 59, N 4 51 Compound 2 mp (Hex/AcOEt 9/1) 103°C IR (CCl_4) $\overline{\nu}$ (SO_2) 1150-1310 and $\overline{\nu}$ (NH) 3260 cm^{-1} ^1H NMR ($CDCl_3$ 200MHz) δ 4 86 (m, 1H, CHN), 5 35 (d, 1H, CHS, J=7 0Hz), 5 65 (d, 1H exchangeable with D_2O NH, J=5 0Hz), 7 36 7 52 (m, 10H**arom**) MS, m/z (relative intensity) 259 (45, M^+), 195 (35, $[M-(SO_2)]^+$), 194 (100, $[M-(SO_2)-(H)]^+$) Anal Calcd for $C_{14}H_{13}NO_2S$ C, 64 84, H, 5 05, N, 5 40 Found C, 64 41, H, 5 19, N 5 16 Compound 3 mp (Hex/AcOEt 8/2) 93°C ^1H NMR ($CDCl_3$, 200MHz) δ 4 97 (m, 1H, CHN) 5 28 (d 1H, CHS, J=6 1Hz) 5 84 (d, 1H, exchangeable with D_2O, NH J=5 8Hz), 7 32-8 26 (m 9H**arom**) MS, m/z (relative intensity) 240 (27 $[M-(SO_2)]^+$), 239 (100, $[M-(SO_2)-(H)]^+$)

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