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DEPROTECTION OF 2-PYRIDYL SULFONYL GROUP FROM PYRIDINE-2-SULFONAMIDES BY MAGNESIUM IN METHANOL

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ABSTRACT

Convenient deprotection of various pyridine-2-sulfonamides prepared by sulfonylation of primary and secondary amines with pyridine-2-sulfonylchloride was achieved by magnesium in methanol at 0°C to the corresponding amines in good yield.

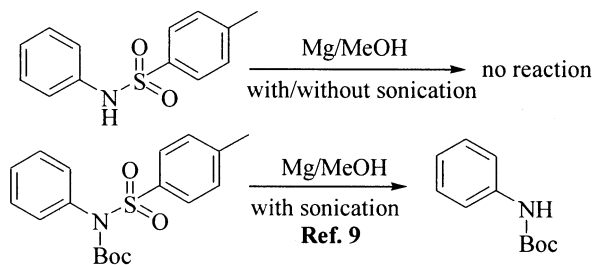
Among a number of amine protection methods, sulfonylation with various substituted phenylsulfonyl chlorides has been widely used since the resulting sulfonamide is usually a crystalline solid and resistant to nucleophilic attack.¹ For the deprotection of a typical *N*-tosyl group, harsh conditions such as sodium in liquid ammonia,² sodium amalgam in a protic solvent,³ sodium naphthalenide,⁴ or refluxing 48% HBr in the presence of phenol⁵ were frequently employed.

Recently, milder deprotection methods including SmI₂,⁶ *n*-Bu₃SnH-AIBN,⁷ electrolysis⁸ and Mg/MeOH under sonication⁹ were reported and complement previous severe conditions. Additional efforts were also made by modifying arenesulfonamide to the more labile heteroarenesulfona-

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mides.^{10,11} These milder methods except for SmI_2 were effective only on sulfonamides activated with an *N*-Boc or *N*-acyl group so they are only applicable to primary amines. For example desulfonylation of *N*-acyl-*N*-phenylbenzenesulfonamide was effected by $n\text{-Bu}_3\text{SnH}$ under neutral conditions, whereas an inactivated secondary sulfonamide like *N,N*-dibenzylbenzenesulfonamide was inert.⁷ Desulfonylation of both *N*-benzenesulfonamides or *N-p*-toluenesulfonamides of primary and secondary amine in refluxing THF in the presence of DMPU (*N,N'*-dimethylpropyleneurea)⁶ was achieved by SmI_2 . Furthermore removal of *N*-pyridine-2-sulfonyl groups in the absence of DMPU at room temperature from the corresponding *N*-pyridine-2-sulfonamides prepared from both primary and secondary amines was reported.¹¹ Recently desulfonylation of doubly activated amines such as *N*-Boc or *N*-acylarenesulfonamide using Mg in methanol under ultrasonic conditions was reported.⁹ Under these conditions parent amines are limited to only primary amines which should be activated by *N*-Boc or *N*-acyl group for desulfonylation. In order to overcome these limitations and to expand the utility of Mg in methanol as desulfonylation reagent,¹² it prompted us to try desulfonylation of primary amine sulfonamide such as *N*-tosylaniline, but it was inert to Mg/MeOH at room temperature even with sonication whereas activated *N*-Boc-*N*-tosylaniline was easily desulfonylated to *N*-Boc aniline (Scheme 1).

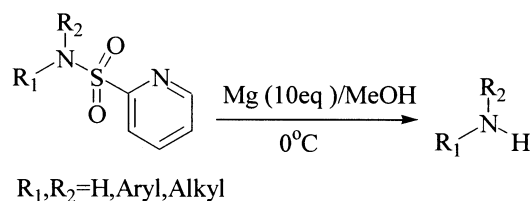
Since *p*-toluenesulfonyl or phenylsulfonyl group of sulfonamide turned



Scheme 1.

out to be an inappropriate for desulfonylation without activation, we were led to find another appropriate sulfonyl group under these conditions. With our previous experience of C-S cleavage,¹² attempts for N-S cleavage were made to desulfonylate pyridine-2-sulfonamides derived from various primary and secondary amines using Mg in methanol (Scheme 2).

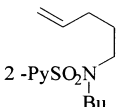
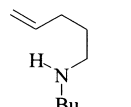

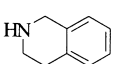

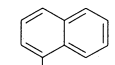




Scheme 2.

In contrast to resistant *p*-toluenesulfonamide desulfonylation proceeded readily to provide the parent amines in good yields.¹³ The results are summarized in Table 1. All the pyridine-2-sulfonamides from alkyl and aryl amines except entries 2 and 4 are prepared by direct sulfonylation of

Table 1. Desulfonylation of Pyridine-2-Sulfonamides by Mg/MeOH

Entry	Pyridine-2-sulfonamide	Yield(%) ^a	Mp(°C)	Time(hr)	Product	Yield(%) ^a
1	2-PySO ₂ NHPh	55	166-167	3	H ₂ NPh	86 ^b
2	2-PySO ₂ N(Ph) ₂	92	129-131	1	HN(Ph) ₂	96
3	2-PySO ₂ NHBn	86	100-101	1.5	H ₂ NBn	77
4	2-PySO ₂ N(Ph)Bn	99	104-105	1	HN(Ph)Bn	93
5	2-PySO ₂ N(Ph)c-Pr	95	74-76		HN(Ph)c-Pr	85
6	2-PySO ₂ N(Ph)c-Pent	72	101-103		HN(Ph)c-Pent	90
7	2-PySO ₂ N(Me)Bn	95	50-52	1.5	HN(Me)Bn	86 ^c
8	2-PySO ₂ N(Bn) ₂	96	78-79	2	HN(Bn) ₂	86
9		85	oil	1.5		80
10	2-PySO ₂ N 	75	108-109	2		81 ^c
11	2-PySO ₂ N 	92	139-141	2		90 ^d
12	N-2-PySO ₂ -L-Phe-Oet	90	99-100	1.5	L-Phe-Ome	64 ^e
13	2-PySO ₂ -Indole	75	52-53	2	Indole	86 ^f
14	2-PySO ₂ NAc(Bn)	91	87-88	2	HNAc(Bn)	47 ^f

^a Isolated yields. ^b Isolated as HCl salt. ^c Isolated as N-Ac derivative. ^d No racemization occurred ^e Isolated as N-Cbz form, [α]_D²⁵ -2.3 (c=1, MeOH). ^f secondary product 2-PySO₂ = pyridine-2-sulfonyl



the parent amines with pyridine-2-sulfonylchloride according to the reported procedures¹¹ and are isolated as stable solids except entry 9. Entries 2 and 4 were prepared by phenylation of pyridine-2-sulfonamides, entry 1 and entry 3, respectively with triphenylbismuth.¹⁴ Although yields are not optimized, desulfonylation proceeded smoothly with 10 equiv Mg at 0°C regardless of the type of amine to give the corresponding parent amines in good yields. In general, reaction rate for desulfonylation was much faster than that of SmI₂ with either *N-p*-toulenesulfonamides (1.5~11 hr)⁶ or 2-pyridinesulfonamides(4 hr).¹² As in the case of pyridine-2-sulfonamides with SmI₂,¹² the rate of desulfonylation does not seem to be much different for sulfonamides derived from primary or secondary amines indicating that steric effects are not critical. Isolation of some amines (entries 7 and 10) was achieved by acetylation after work up due to their high polarity. By control experiments subjecting pyridine-2-sulfonamides to methanolic Mg(OMe)₂ solution in which no reaction takes place, possibility of desulfonylation via methanolysis under the reaction conditions was eliminated. Thus we assumed that desulfonylation occur via single electron transfer to form a putative radical intermediate. In an attempt to trap the aminyl radical which might be formed in the course of an electron transfer reaction, *N*-butyl-*N*-1-penten-5-ylaminesulfonamide (entry 9) was subjected to the reaction conditions hoping to obtain substituted pyrrolidine as radical cyclization product,^{12,15} but it only resulted in desulfonylation product. Chiral amine sulfonamides (entry 11 and 12) were subjected to the reaction condition. No racemization was observed for entry 9, however, partial racemization ($[\alpha]_D -2.3$ (c=1, MeOH), 16% e.e.) and ester exchange were observed for entry 12. In order to measure optical yield the deprotected ester was converted to its *N*-Cbz form and compared with literature value.¹⁶ In contrast to the previously reported selective desulfonylation of TsNAc(Bn) to give HNAc(Bn) under sonication condition,⁹ that of pyridine-2-sulfonamide(entry 14) proceeded deacetylation first to provide 2-PySO₂NHBn followed by desulfonylation like entry 3 to give BnNH₂.¹⁷ We could verify that it is from methanolysis by subjecting the sulfonamide to methanolic solution of Mg(OMe)₂ to obtain 2-PySO₂NHBn as a single spot in TLC. However, we could isolate the desulfonylated product HNAc(Bn) in 47% yield which must be formed from reaction of benzyl amine and methylacetate in the reaction mixture.

In conclusion, regardless of primary or secondary amine the corresponding stable solid pyridine-2-sulfonamides were conveniently desulfonylated with Mg in methanol. It is apparent that 2-pyridinesulfonyl group can be used as a convenient amine protecting group in case Mg in methanol is employed for desulfonylating reagent.



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13. General Procedure: A solution of *N,N*-diphenylpyridine-2-sulfonamide (155 mg, 0.5 mmol) in dry methanol (4 ml) was added to Mg powder (122 mg, 5 mmol) in an ice bath. The reaction mixture was stirred for 2 hr under a nitrogen atmosphere until the substrate disappeared by TLC. To the reaction mixture equal volumes of diethyl ether and saturated aqueous NH₄Cl were added and the whole mixture was stirred for 2 hr. The organic layer was separated and the aqueous layer washed with ether. The combined organic layers were dried over MgSO₄ and then concentrated *in vacuo* to give 81 mg (96%) of diphenylamine in almost pure form.
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