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Can we aminate Grignard reagents under Barbier conditions?

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Abstract—The reaction of aryl bromides with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime and magnesium in THF at reflux temperature for 3 h provides a one-pot procedure for amination of aryl Grignard reagents under Barbier conditions.

The formation of C–N bonds using electrophilic amination reagents is gaining importance due to the commonplace use of organometallic reagents and the importance of amino functionalities in natural products and drugs as well as building blocks in organic synthesis. There are detailed reviews on the amination of carbanions.[1]

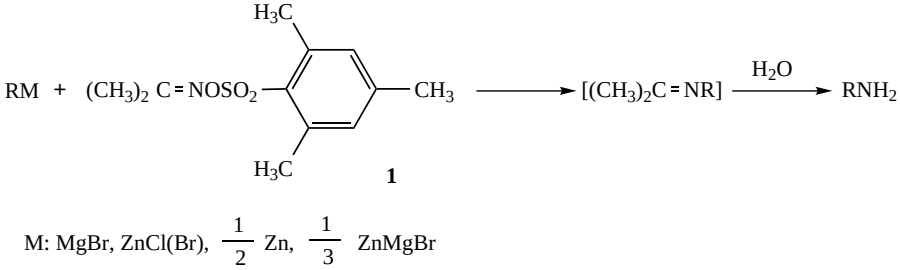
Recent studies in this field have found several new electrophilic amination reagents, such as lithium *t*-butyl *N*-tosyloxycarbamate,[2] ceric ammonium nitrate/sodium azide,[3] *N*-(tosylimino)phenyliodinane,[4] diethyl *N*-anisyliminomalonate,[5] new derivatives of *O*-substituted hydroxylamines,[6] *N*-protected aziridines,[7] and oxime *O*-sulfonates.[8]

Efficient methods are now available for electrophilic amination of organolithiums,[1,2a] Grignard reagents,[1,2a,5,8a,b,e,f] organocuprates,[1,2a,6,8a,c,d,f] organozincs,[8c,d,9,10] and enolates.[1,2b,3,4,7,11]

In addition, successful asymmetric versions of electrophilic amination using chiral Grignard reagents[12] and chiral enolates[2b,13] or using enolates in the presence of chiral catalysts[14] or stereocontrolling units[15] have been reported. Azodicarboxylate esters have been used extensively as aminating reagents for this purpose. Chiral azodicarboxylate esters[16] and azo dicarboxamides[17] have also been synthesized for the electrophilic amination of achiral enolates.

Acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime **1** has been developed in our laboratories for the electrophilic amination of Grignard reagents and organozincs.

Reaction of mono or diorganozincs and triorganozincates with **1** in THF in the presence of CuCN at room temperature for 3 h resulted in the amination of the organozincs in moderate to good yields. As organozincs can be prepared by transmetallation of the corresponding Grignard reagents and organolithiums, this amination protocol also provides an alternative method for electrophilic amination of Grignard reagents and organolithiums. In earlier papers,[8a,b,18] we reported a method for the amination of aryl Grignard reagents with **1** in THF:toluene in the presence of CuI as a



Scheme 1. Amination of organomagnesium and organozinc reagents with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime.

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catalyst or $MgCl_2$ as a Lewis acid at reflux temperature for 11–23 h.

In amination, **1** reacts with organomagnesium and organozinc reagents by displacement of the mesitylsulfonyl group giving an imine, which upon hydrolysis provides amines (Scheme 1).

In an effort to broaden the scope of electrophilic amination with **1**, we investigated the feasibility of the reaction under Barbier conditions,[19,20] i.e. we tried to carry out the reactions of organic halides with magnesium in the presence of **1**. Although the use of previously prepared Grignard reagents does not pose any practical problem in Cu(I) catalyzed electrophilic amination, the reaction of in situ prepared Grignard reagents with **1** is, by all means, more pleasing. To this end, we examined the reactivities of some aryl bromides, *n*-hexyl, cyclohexyl and benzyl bromide in the Barbier–Grignard type amination procedure.

The synthesis of arylamines was achieved with remarkable ease by simultaneous addition of THF solutions of the aryl bromide and **1** to magnesium and then heating the mixture under reflux for about 3 h. The yields of arylamines obtained in the reactions of aryl bromides with magnesium and **1**[21] are tabulated (Table 1) and the yields of the reactions of aryl Grignard reagents with **1** under catalytic conditions[8a,b,18] are also included for comparison. As can be seen, Barbier conditions provide arylamines in moderate yields, which are not lower than those obtained with pre-prepared Grignard reagents. In addition, amination of in situ prepared Grignard reagents took place without a co-solvent and in a much shorter time, and to our surprise without Cu(I) catalysis or $MgCl_2$ addition. However, we could not succeed in the amination of *n*-hexyl, cyclohexyl and benzyl magnesium bromides under Barbier conditions and the yields of amines were found to be no higher than 15%. We would also like to note that our earlier attempts[18] in the amination of pre-prepared *n*-hexyl and benzyl Grignard reagents with **1** either in the presence of CuI or $MgCl_2$ catalysis or without catalysis did not give yields higher than 22%. So, to our satisfaction, the reaction of aryl bromides with magnesium and acetone *O*-(2,4,6-trimethylphenylsulfonyl) oxime in THF at reflux temperature provides a versatile route for the synthesis of arylamines via a Barbier–Grignard type amination.

Efforts to extend the magnesium mediated electrophilic amination of organic halides are currently in progress.

Table 1. Comparative amination of pre-prepared and in situ prepared aryl Grignard reagents (Methods A and B, respectively) with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime **1**

Method A[a]

$$ArBr \xrightarrow[THF]{Mg} ArMgBr \xrightarrow[2.\ conc.\ HCl,\ reflux,\ 2–4\ h\ and\ rt,\ 24\ h]{1.\ \mathbf{1}\ Catalyst,\ Et_2O:toluene\ (1:4),\ 75°C,\ 11–23\ h} ArNH_2$$

Catalyst: CuI, $MgCl_2$

Method B[b]

$$ArBr + Mg + \mathbf{1} \xrightarrow[2.\ conc.\ HCl,\ rt,\ 24\ h]{1.\ THF,\ 75°C,\ 3\ h} ArNH_2$$

Entry	R	Yield of $ArNH_2$ (%)[c]	
		Method A	Method B
1	C_6H_5	59[d]	52
2	C_6H_5	56[e]	–
3	4-$CH_3C_6H_4$	56[f]	53
4	4-$CH_3OC_6H_4$	38[e]	56
5	1-$C_{10}H_7$	2[e]	40

[a] Refs. 8a,b,18.
[b] Ref. 21.
[c] Yield of amine isolated as its *N*-benzoyl derivative.
[d] In the presence of 10 mol% CuI.
[e] In the presence of 20 mol% $MgCl_2$.
[f] In the presence of 10 mol% $MgCl_2$.

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21. **Typical procedure**: Under a nitrogen atmosphere and at room temperature, to a dry reaction flask provided with a reflux condenser and two addition funnels containing THF solutions of aryl bromide (6 mmol in 6 ml THF) and **1** (0.765 g, 3 mmol in 6 ml THF) was added magnesium (0.173 g, 7.2 mmol). After heating the flask, the reaction was started by adding about 1 cm^3 of a THF solution of aryl bromide and if necessary, the magnesium was activated with a few crystals of iodine or one or two drops of 1,2-dibromoethane. While stirring, the solutions were added simultaneously at a rate which does not stop the reaction. Following the addition period of about 15–20 minutes, the reaction mixture was refluxed at 75°C for 2.5–3 h. For hydrolytic work-up, conc. HCl (10 cm^3) was added and the reaction mixture was stirred at room temperature overnight. The aqueous phase was washed with diethyl ether, made basic with conc. NaOH solution and the free amine was extracted with diethyl ether (3×50 cm^3). The organic layer was dried over Na_2SO_4. After evaporation of the solvent, the product amines were converted to their *N*-benzoyl derivatives as already described and their melting points and spectral analyses were found to match those already reported.[8d]