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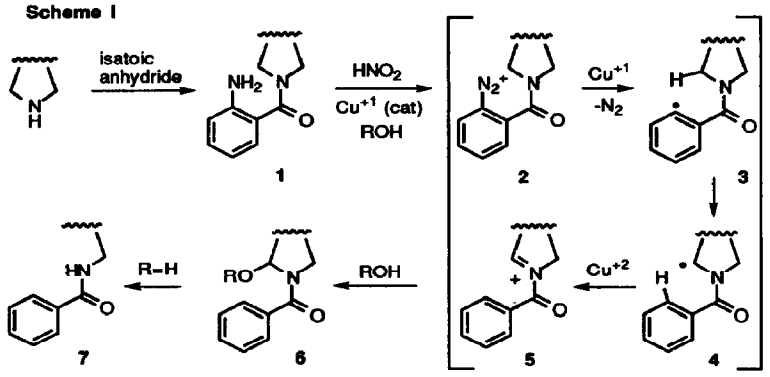
A Convenient Synthetic Method for Amide Oxidation

Gyoonhee Han, Matthias C. McIntosh, and Steven M. Weinreb*
Department of Chemistry
The Pennsylvania State University
University Park, PA 16802

Summary: Diazotization of *o*-aminobenzamides in methanol in the presence of a catalytic amount of CuCl affords α-methoxybenzamides in good yields.

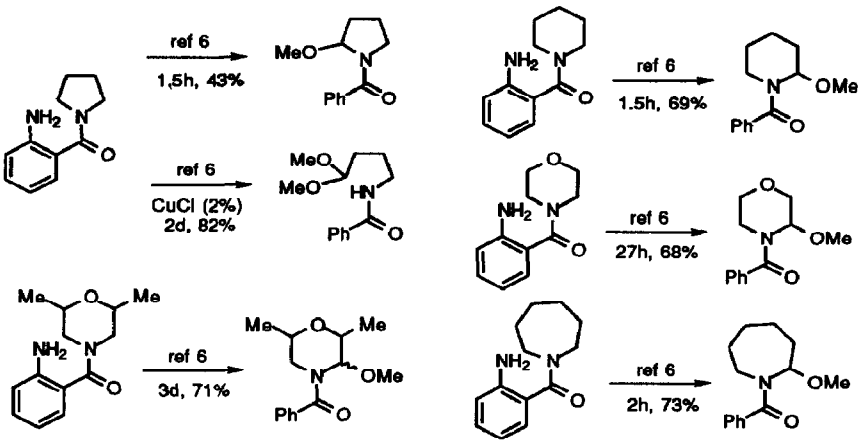
In the course of some ongoing projects in alkaloid total synthesis involving N-acyl imine chemistry, we required a procedure for amide oxidation and sought a convenient alternative to the electrochemical methodology pioneered by Shono.[1] A number of years ago Hey and coworkers reported the dealkylation of *o*-diazobenzamides in the presence of copper.[2] Subsequent mechanistic studies by Cohen, *et al.*[3,4] established that this transformation proceeds via the pathway shown in **Scheme I**. Thus, diazonium salt **2** is first reduced by cuprous ion to aryl radical **3**. 1,5-Hydrogen transfer in **3** then affords radical **4** which is oxidized by cupric ion to N-acyl iminium complex **5**. Hydrolysis of **5** via **6** leads to the observed dealkylation product **7**. We considered the possibility of developing this interesting transformation into a synthetically useful amide oxidation procedure and in this communication we outline the results of these studies.

Scheme I



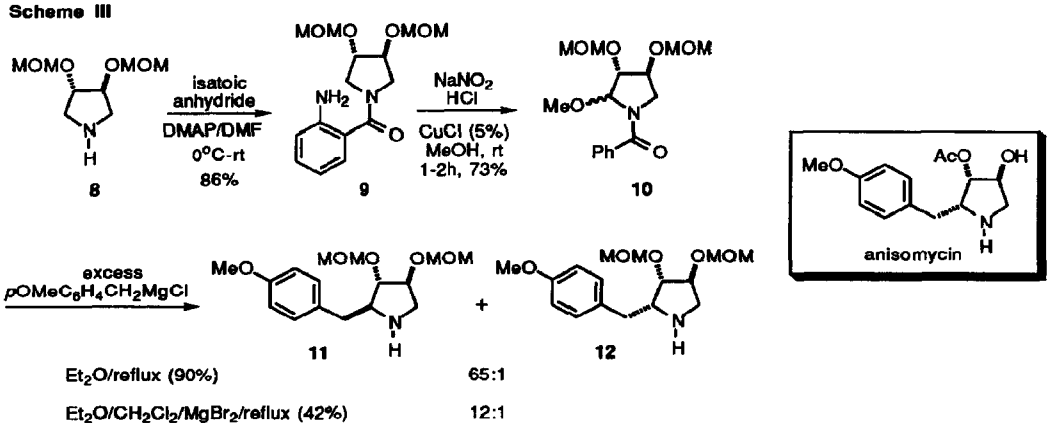
Secondary amines can be converted into *o*-aminobenzamide derivatives in high yields using isatoic anhydride (**Scheme I**).[5] We have found that diazotization of compounds **1** in dry methanol in the presence of a catalytic amount of cuprous chloride yields α-methoxybenzamides **6** (R=Me) in good yields.[6] A number of examples of this sequence using various symmetrical amines are shown in **Scheme II**. In the case of the pyrrolidine-derived system, there was a tendency for ring opening of the initial α–methoxyamide to occur, yielding the correspondence amido dimethyl acetal.

Scheme II



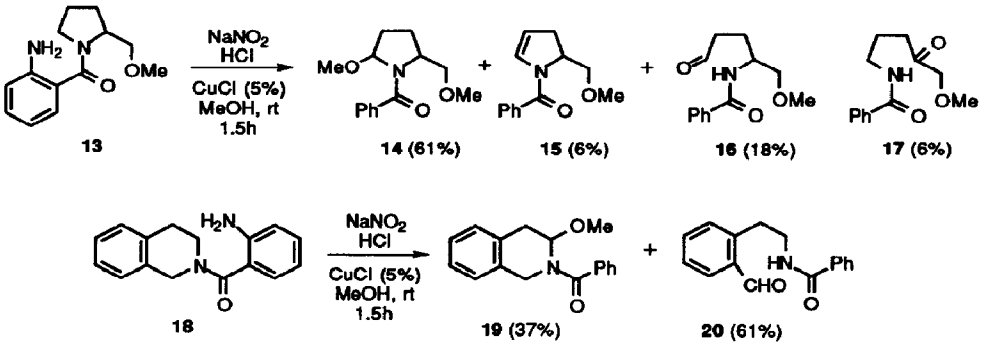
We next attempted to utilize this methodology in a synthesis of the antibiotic anisomycin (**Scheme III**).[7] Therefore, known pyrrolidine derivative **8**, which is readily prepared from L-tartaric acid,[8] was first converted to *o*-aminobenzamide **9**. Subsequent application of the above oxidation procedure to **9** then afforded the α–methoxybenzamide **10** in good yield. However, addition of 5 equivalents of *p*-methoxybenzylmagnesium chloride to **10** unfortunately provided mainly the undesired *anti* alkylated pyrrolidine **11**, along with only a trace of *syn* isomer **12** (65:1 ratio). This reaction presumably occurs via the intermediacy of an electrophilic N-acyl iminium compound and addition of the Grignard reagent to this species occurs *anti* to the large OMOM group. Performing the reaction in the presence of $MgBr_2$ in an attempt to improve the relative amount of the desired *syn* chelation-controlled addition product had only a slight effect on the ratio. These results are somewhat surprising since a very closely related nitrone[8a] was found to give primarily *syn* addition of *p*-methoxybenzylmagnesium chloride when catalyzed by $MgBr_2$.

Scheme III



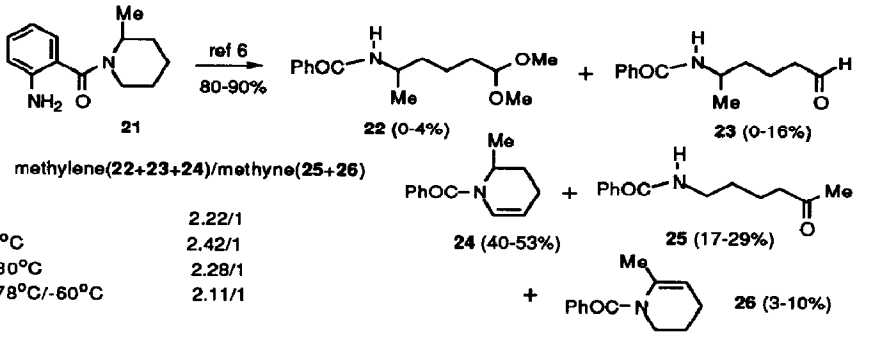
The oxidation reaction has also been investigated with some unsymmetrical amides to probe the regioselectivity of the process. Subjection of amide **13** to the standard diazotization conditions[6] afforded a mixture of oxidation products **14-17** in excellent overall yield (**Scheme IV**). Thus, the ratio of methylene to methine H-atom abstraction is ~14:1. With unsymmetrical amide **18**, two products **19** and **20** were obtained, although in this case the ratio of benzylic methylene to alkyl methylene abstraction was only about 1.7:1. Cohen, *et al.* have found that in this type of free radical reaction (cf **Scheme I**) hydrogen atom abstraction is much faster than amide bond rotation,[3,9] and thus initial amide conformation is probably the governing factor in determining the regiochemistry of the reactions shown in **Scheme IV**.

Scheme IV



A series of experiments was conducted to determine the effect of the temperature at which the reaction is run upon regiochemistry. The 2-methylpiperidine-derived amide **21** was examined as shown in **Scheme V.** Although small differences in product composition were observed at different temperatures, somewhat surprisingly the ratio of methylene hydrogen abstraction products (**22-24**) to methine abstraction products (**25-26**) was essentially invariant. We are continuing to investigate the scope and some applications of this methodology.[10]

Scheme V



methylene(22+23+24)/methyne(25+26)	
rt	2.22/1
0°C	2.42/1
-30°C	2.28/1
-78°C/-60°C	2.11/1

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References and Notes

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4. For a related process, see: Pines, S. H.; Purick R. M.; Reamer, R. A.; Gal, G. *J. Org. Chem.* **1978**, 43, 1337.
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6. General Experimental Procedure: To a 0.05 M solution of the *o*-aminobenzamide in methanol was added 2 equivalents of $NaNO_2$ and 5 mol % of CuCl. Methanolic HCl (3%, 4.5 equiv) was added over 5-10 min and the reaction mixture was stirred at rt for the time indicated in **Scheme II**. Saturated $NaHCO_3$ was added and MeOH was removed *in vacuo*. The residue was extracted with EtOAc which was washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by preparative tlc (EtOAc/hexanes, 1/2-1/1).
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