

A SIMPLE AND CONVENIENT SYNTHESIS OF PSEUDOEPHEDRINE FROM N-METHYLAMPHETAMINE

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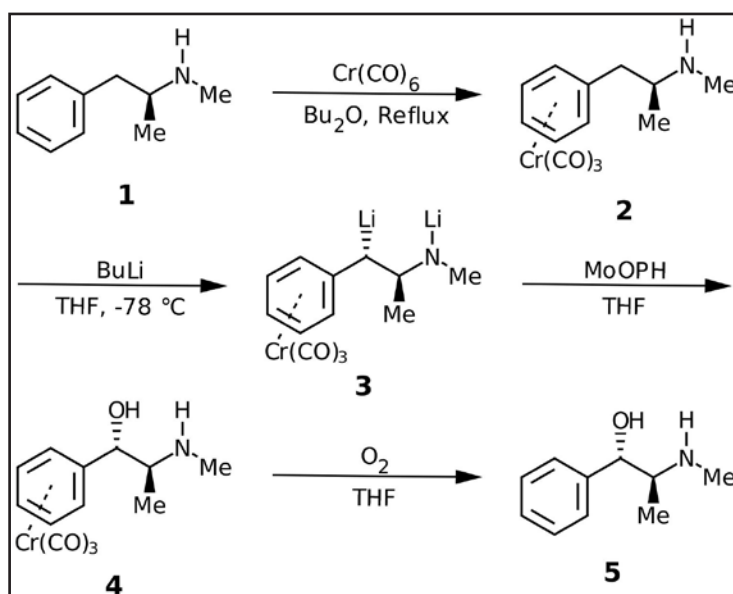
Pseudoephedrine, active ingredient of Sudafed®, has long been the most popular nasal decongestant in the United States due to its effectiveness and relatively mild side effects¹. In recent years it has become increasingly difficult to obtain pseudoephedrine in many states because of its use as a precursor for the illegal drug N-methylamphetamine (also known under various names including crystal meth, meth, ice, etc.)^{1,2}. While in the past many stores were able to sell pseudoephedrine, new laws in the United States have restricted sales to pharmacies, with the medicine kept behind the counter. The pharmacies require signatures and examination of government issued ID in order to purchase pseudoephedrine. Because the hours of availability of such pharmacies are often limited, it would be of great interest to have a simple synthesis of pseudoephedrine from reagents which can be more readily procured.

A quick search of several neighborhoods of the United States revealed that while pseudoephedrine is difficult to obtain, N-methylamphetamine can be procured at almost any time on short notice and in quantities sufficient for synthesis of useful amounts of the desired material. Moreover, according to government maintained statistics, N-methylamphetamine is becoming an increasingly attractive starting material for pseudoephedrine, as the availability of N-methylamphetamine has remained high while prices have dropped and purity has increased². We present here a convenient series of transformations using reagents which can be found in most well stocked organic chemistry laboratories to produce pseudoephedrine from N-methylamphetamine.

While N-methylamphetamine itself is a powerful decongestant, it is less desirable in a medical setting because of its severe side effects and addictive properties³. Such side effects may include insomnia, agitation, irritability, dry mouth, sweating, and heart palpitations. Other side effects may include violent urges or, similarly, the urge to be successful in business or finance.

In our search for sources of N-methylamphetamine we have found that, similar to research grade chemicals purchased from the major chemical supply houses, the purity of the reagent varies greatly between suppliers and even between batches despite the above cited overall increase in purity. Unfortunately, and again similar to suppliers of fine chemicals, relative cost is not strongly correlated to sample quality. We therefore found it necessary to purify the starting material before use. This may be accomplished by precipitating the amphetamine from isopropanol with

HCl followed by deprotonation with sodium hydroxide and extraction into chloroform, which after removal of the solvent in vacuo yields N-methylamphetamine, 1. In the majority of the samples obtained for this study, 1 was greater than 95% enantiomerically pure, with the S enantiomer being the major isomer present. This is consistent with reduction of commercially available ephedrine or pseudoephedrine as the origin of the casually procured material used in this study.



Scheme 1 Synthesis of pseudoephedrine from N-methylamphetamine.

The synthetic procedure is shown in scheme 1. The chromium tricarbonyl coordination compound **2** was formed in 96% yield by heating the purified starting material and chromium hexacarbonyl in dibutyl ether solution according to the procedure described by Blagg and Davies⁴. While in the cited work a single equivalent of $^n\text{BuLi}$ was used to deprotonate a similar chromium complex, in the case of **2** two equivalents of $^n\text{BuLi}$ were required due to the presence of the relatively acidic amine proton. After successful formation of the dianion **3**, which was not isolated but taken on immediately in the same reaction vessel, a single hydroxy group was introduced at the alpha position by addition of one equivalent of oxodiperoxymolybdenum(pyridine) (HMPA), commonly known as MoOPH. The series of transformations producing **4** from **2** went in 87% yield overall. Chromium was de-complexed from the newly formed alcohol **4** by exposing the reaction mixture to air.

After washing the resulting solution with dilute NaOH and DI water crude pseudoephedrine **5** was obtained. Purification was accomplished by recrystallization of the material from toluene followed by precipitation from isopropanol with HCl to obtain the final product **5***HCl in 93% yield from **4**. The hydrochloride and sulfate salts are the most commonly encountered forms of pseudoephedrine in pharmaceutical preparations and thus **5***HCl can be used as-obtained from the precipitation.

This synthesis follows that of Blagg and Davies, who used *N,N*-dimethylamphetamine as the starting material and produced the (1*S*,2*S*)-diastereomer of *N,N*-dimethyl pseudoephedrine exclusively. This, as discussed in their publication, is likely due to coordination of lithium in the intermediate complex by the nitrogen atom. In the current study both the alpha carbon and the nitrogen atom are deprotonated and it was thought that charge repulsion may decrease, or even reverse, the diastereoselectivity of the reaction. On the contrary, the selectivity was retained in this reaction, resulting in pure (1*S*,2*S*)-pseudoephedrine.

We have demonstrated here a simple series of transformations which allow pseudoephedrine to be obtained in a more straightforward manner than is the current norm. We expect that the simultaneous trends of restricting pseudoephedrine sales while *N*-methylamphetamine becomes

less expensive and of higher purity will make the methods presented here increasingly attractive. Future work will focus on increasing yields and decreasing reaction times. It was also suggested to one of us that a “green chemistry” approach, that is, elimination of toxic and environmentally detrimental solvents and reagents, should be a high priority⁵. We agree and plan to look for alternative reagents to replace the chromium based material as well as the ether solvents.

Notes

1. “Oral Phenylephrine: An Ineffective Replacement for Pseudoephedrine?” L. Hendeles and R.C. Hatton, *Journal of Allergy and Clinical Immunology*, vol. 118, 2006, pp. 279–80.
2. <http://www.justice.gov/ndic/pubs38/38661/meth.htm> accessed Feb. 23rd 2012.
3. “Clinical Effects and Management of Methamphetamine Abuse,” F. Romanelli and K.M. Smith, *Pharmacotherapy*, vol. 26, no. 8, August 2006, pp. 1148-56.
4. “Stereospecific Conversion of *N,N*-dimethylamphetamine into *N*-methylpseudoephedrine,” Julian Blagg and Stephen G. Davies, *Journal of the Chemical Society, Chemical Communications*, vol. 10, 1985, pp. 653-4.
5. Private communication.

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