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IODINATION OF METHOXYAMPHETAMINES WITH IODINE AND SILVER SULFATE.

Wing-Wah Sy

Pharmaceutical Chemistry Division, Bureau of Drug Research, Health Protection Branch, Health and Welfare Canada. Tunney's Pasture, Ottawa, Ontario, Canada K1A 0L2.

Abstract: **Iodination of methoxyamphetamines with iodine/silver sulfate at room temperature gives iodomethoxyamphetamines in good yield.**

Radioiodo-labelled amphetamines are widely used in brain imaging and therefore are of great value in medicinal chemistry. The synthesis of iodoamphetamine is difficult because iodine is the least reactive halogen in electrophilic aromatic substitution.[1] Also, because the amine group can interfere in a number of reactions such as oxidative halogenation; protection of the amine group is usually required for the iodination procedure. Iodoamphetamines have been synthesized by the use of ICl,[2] chloramine T,[3] silver trifluoroacetate,[4] iododediazotization[5] and iododeboration.[6]

It was reported that direct iodination of 2,5 dimethoxy-N,N-dimethylamphetamine by chloramine T was unsuccessful because the ring is not sufficiently activated.[3a] An attempt to iodinate the 2,5 dimethoxyamphetamine by ICl resulted in an oxidative attack on the amine group.[2b] A low yield was obtained by direct iodination of the N-acetyl derivative of 2,5-dimethoxyamphetamine with iodine and silver trifluoroacetate.[4]

Recently, it was found in our laboratories that iodine / silver sulfate is an excellent iodination reagent. This reagent has been used for iodinating alkyl and alkoxybenzenes,[7] aromatic amines[8] and uridines.[9]

The iodine / silver sulfate system has now been applied to the syntheses of iodomethoxyamphetamines. The results are presented in this report.

Methoxyamphetamines can be iodinated with iodine / silver sulfate at room temperature in ethanol (scheme 1). Protecting the amino group is not necessary under these conditions, and high yields are obtained. However, under similar conditions, there is no reaction with methylamphetamines or amphetamine.

Results are summarized in Table 1.

A representative iodination was performed as follows:

4-methoxyamphetamine (165 mg, 1mM) was added to a mixture of iodine (508 mg, 2mM) and silver sulfate (622 mg, 2mM) in ethanol (20 mL) at room temperature. The mixture was stirred for 17 hours. After this time, the yellow solid was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue

was dissolved in chloroform and washed with aqueous 5% NaOH solution, then with water. After separation, the organic layer was dried over sodium sulfate and evaporated to dryness. The residue was chromatographed on silica gel and eluted with 8% ethanol / chloroform to give pure 3-iodo-4-methoxyamphetamine (250 mg, 86%).

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TABLE 1

Iodination of Methoxyamphetamines with Iodine and Silver Sulfate

Substrate[10] (Amphetamine)	Yield (%)	Product[11] (Amphetamine)
2-Methoxy-	83	5-Iodo-2-methoxy-
3-Methoxy-	77	2-Iodo-5-methoxy-
4-Methoxy-	86	3-Iodo-4-methoxy-
2,4-Dimethoxy-	80	2,4-Dimethoxy-5-iodo-
2,5-Dimethoxy-	78	2,5-Dimethoxy-4-iodo
2,6-Dimethoxy-	84	2,6-Dimethoxy-3-iodo
3,5-Dimethoxy-	88	3,5-Dimethoxy-2-iodo

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