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Preparation of 3-Amino-1,4-Benzodiazepin-2-Ones Via Direct Azidation with Trisyl Azide

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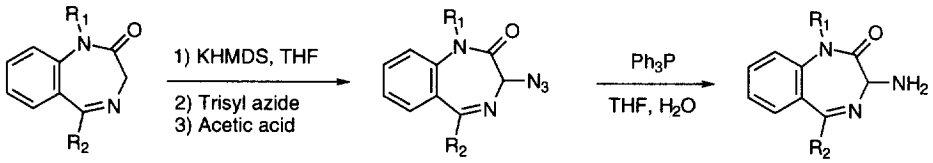
Abstract: An efficient synthesis of 3-amino-1,4-benzodiazepin-2-ones utilizing triisopropylbenzenesulfonyl azide (trisyl azide) for the direct azidation of 1,4-benzodiazepin-2-ones is described. Copyright © 1996 Elsevier Science Ltd

Benzodiazepines enjoy a privileged structure status in medicinal chemistry, with derivatives shown to have activity against a wide range of biological targets.[1,2,3] Recently, compounds derived from 3-aminobenzodiazepines have demonstrated utility as CCK-A[4,5] and CCK-B[6] receptor antagonists. Interest in these laboratories in benzodiazepines as CCK-antagonists has led to several strategies for the synthesis of 3-amino-5-phenyl-1,4-benzodiazepin-2-ones.[7] Previous work established that introduction of an amine into the 3-position of 5-phenyl-1,4-benzodiazepin-2-ones can be effectively accomplished using a two step procedure via the oxime.[8] Anion formation followed by quenching with isoamyl nitrite and subsequent catalytic hydrogenation of the resulting oxime to the amine proceeded in good overall yield.

Recently our attention turned to the corresponding reaction utilizing 5-alkyl-1,4-benzodiazepin-2-ones. The starting materials (**1a-f**) were prepared by established literature procedures,[8,9,10] however amination as described above proceeded with problems associated with both the oxime formation and overreduction of the benzodiazepine imine during hydrogenation. Alternative bases and reduction conditions were investigated without significant improvement. Therefore, we decided to examine other methods for the introduction of amine functionality into the benzodiazepin-2-one ring system which may yield 3-aminobenzodiazepines in good yield and without necessitating a hydrogenation step.

Direct azidation of enolates has been reported,[11] however we were concerned that the increased acidity of the benzodiazepine would lead to at least some diazo transfer products. Treatment of the benzodiazepines (**1a-f**) with 1.2 eq. potassium bis(trimethylsilyl)amide and quenching with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) afforded the 3-azidobenzodiazepines (**2a-f**). We saw no evidence of any 3-diazobenzodiazepine formation resulting from diazo transfer. This is in agreement with the work of Evans[11]

but contrasts with earlier reports on the use of trisyl azide for diazo transfer.[12] Reduction of the azides (**2a-f**) to the amines (**3a-f**) was accomplished either via catalytic hydrogenation or preferably using milder triphenylphosphine/H_2O/THF conditions[13] thereby eliminating problems associated with overreduction of the benzodiazepine ring.



1 **2** **3**

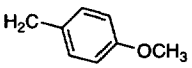
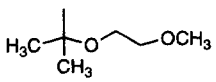
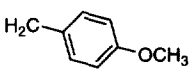
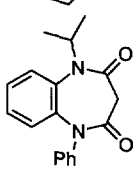
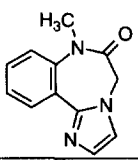
This procedure is also applicable to the preparation of 3-amino-5-phenyl-1,4-benzodiazepines (**3g-j**) and results in a 15-20 % increase in yield of amine over the previously described method.[8] In addition, to test the scope of this method the azidation procedure has been used to prepare the amines of the 1,5-benzodiazepin-2,4-dione (entry 4) and the imidazobenzodiazepine derivative (entry 5). Since previous examples of direct azidation mainly involved ester or imide enolates these results serve to expand the range of substrates which undergo azidation without competing diazo transfer.

In conclusion, an efficient synthesis of 3-amino-1,4-benzodiazepin-2-ones via direct azide transfer has been developed. This simple two step procedure results in high overall yields of amines and provides an avenue for the preparation of multi-gram quantities of 5-alkyl-3-amino-1,4-benzodiazepin-2-ones (**3a-f**).

In a typical procedure 1-methyl-5-isopropylbenzodiazepin-2-one **1a** (200 mg, 0.925 mmole) in THF (6 ml) at -78°C was treated with 0.5 M potassium bis(trimethylsilyl)amide in toluene (2.1 mL, 0.971 mmole) followed after 5 minutes by a solution of trisyl azide (0.715 g, 2.30 mmole) in THF (7 mL). After 5 minutes stirring at -78°C, acetic acid (0.233 mL, 4.07 mmole) was added and the reaction warmed to 30 °C for 2 hours. Aqueous sodium bicarbonate (10 mL) was added and the product extracted into methylene chloride. Concentration and chromatography (silica, ethyl acetate/hexane-1:2) gave 205 mg azide **2a** , 86%. Treatment of a solution of **2a** (100 mg, 0.389 mmole) in THF (1 mL) and water (70 uL) with triphenylphosphine (306 mg, 1.17 mmole) for 24 hr at room temperature followed by extractive work up gave 86 mg amine **3a**, 97%.

Alternate procedure using potassium t-butoxide: 1-(2,2,2-trifluoroethyl)-5-isopropylbenzodiazepin-2-one **1f** (50.0 g, 0.176 mole) in THF (1.25 L) at -78°C was treated with 1.0 M potassium t-butoxide in THF (361 mL, 0.361 mole) followed after 5 minutes by a -78°C solution of trisyl azide (60 g, 0.194 mole) in THF (600 mL). After 5 minutes stirring at -78°C, acetic acid (45 mL, 0.774 mole) was added and the reaction warmed to 30°C for 2 hours. Aqueous sodium bicarbonate (1.0 L) was added and the product extracted into methylene chloride (2.0 L). Concentration and chromatography (silica, ethyl acetate/hexane-1:3) gave 53.8 g azide **2f**, 94%. Treatment of a solution of **2f** (50 g, 0.154 mole) in THF (500 mL) and water (28 mL) with triphenylphosphine (121.0 g, 0.461 mole) for 24 hr at room temperature followed by extractive work up gave 43.7 g amine **3f**, 95%.

TABLE 1 Preparation of 3-Aminobenzodiazepines

Entry	R_1	R_2	Yield azide (%) [a]	Yield amine (%) [a]	Reduction method [b]
1a	CH_3		86	97	A
1b			84	80	B
1c	CH_3		81	80	B
1d	CH_3	CH_2CH_3	83	95	A
1e	CH_3	$CH_2CH_2CH_3$	76	93	A
1f	CF_3CH_2		50 [c] 94 [d]	95	A
1g	CH_3	Ph	88	96	A
1h		Ph	89	92	A
1i	CF_3CH_2	Ph	77 [c]	91	A
1j		Ph	89	88	A
4			98	92	A
5			77	95	A

a) All products were characterized by the appropriate spectral and analytical means and when available compared to authentic materials. b) Reduction methods: A) Triphenylphosphine (3eq.), H_2O(10eq.), THF; B) 10% Pd/C, acetic acid, hydrogen, 1atm. c) Lower yields were attributed to the loss of HF from the trifluoroethyl group during enolate formation when using Potassium Bis(trimethylsilyl)amide. The corresponding 1-(2,2-difluoroethylene)-3-azidobenzodiazepine-2-one byproduct was isolated by chromatography and characterized. d) Substitution of Potassium t-butoxide (2.05 eq.) for KHMDS for enolate formation resulted in improved yields of azide and no elimination byproducts.

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