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Vicarious nucleophilic substitution of 1-benzyl-5-nitroimidazole, application to the synthesis of 6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one

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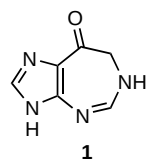
Abstract—Reaction of 1-benzyl-5-nitroimidazole with carbanion generated from chloroform and potassium *tert*-butoxide afforded 1-benzyl-4-dichloromethyl-5-nitroimidazole in 72% yield. This vicarious nucleophilic substitution reaction was successfully applied to the synthesis of 6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one, an important intermediate in the synthesis of natural and biologically active compounds.

6,7-Dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one is an important intermediate in organic synthesis.[1–7] For example, it was used in the synthesis of pentostatin[1–3] and coformycin,[4] both naturally occurring anticancer and antiviral nucleosides. More recently, 6,7-dihydroimidazo-[4,5-*d*][1,3]diazepin-8(3*H*)-one found wide application in the synthesis of a variety of other biologically important and medicinally useful agents.[7]

Previously, 6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one **1** was prepared in eight steps from 4-methyl-5-nitroimidazole through a mixture of intermediates, 1- and 3-benzyl-4-styryl-5-nitroimidazole, **2** and **2′**.[1,3] While this method was developed for multigram scale synthesis, it was limited by the use of hazardous gases (O_3, H_2S, H_2), the supply of the starting material, and other problems.[8] In one of our drug discovery programs, we required an easy access to large amounts of compound **1**. Herein, we describe a new improved method for synthesis of this molecule.



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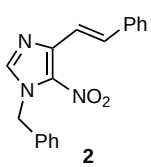

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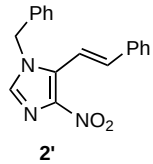

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Our synthesis of 6,7-dihydroimidazo[4,5-*d*][1,3]-diazepin-8(3*H*)-one **1** starts with the readily available and less expensive starting material, 4-nitroimidazole **3** (Scheme 1). Treatment of **3** with benzyl chloride in DMF in the presence of potassium carbonate afforded 1-benzyl-5-nitroimidazole **4** in 98% yield.[9,10] Vicarious nucleophilic substitution reaction[11] of **4** with the anion generated from chloroform and potassium *tert*-butoxide afforded 1-benzyl-4-dichloromethyl-5-nitroimidazole **5** in 72% yield.[10,12] Hydrolysis of **5** with formic acid followed by treatment of the resulting aldehyde with $NaClO_2/NH_2SO_3H$[13] gave the carboxylic acid **6** in 87% yield.[3,10] Compared to the previous synthesis of **6**,[3] the new method not only eliminates the use of the unfriendly ozone, but also is more cost-effective by using less expensive starting material **3**.

Coupling the acid **6** with nitromethane using CDI following literature conditions gave the dinitro ketone **7** in 54–68% yield.[3,10] To avoid palladium poisoning by residual sulfides in the deprotection of **8** to **9**,[8] we decided to use Fe/HCl[14] instead of tin chloride for the reduction of **7** to **8**. The new reaction proceeded extremely well under the new conditions, giving the desired product **8** in 95% isolated yield.[10] Another important modification was also made for improved scalability, i.e. HCO_2NH_4 was used instead of H_2 in the transformation of **8** to **9**. Under the new reaction conditions, compound **9** was obtained in 99% yield.[3,10] Finally, treatment of **9** with ethyl formate in DMSO afforded final product **1**, which was isolated as a mono hydrochloride salt and mono DMSO solvate in 81% yield.[3,10]

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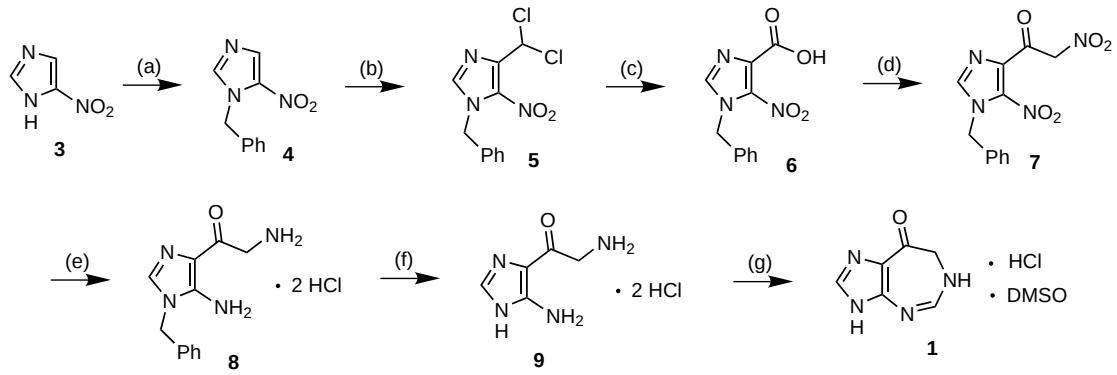

Scheme 1. *Reagents and Conditions*: (a) $PhCH_2Cl$, K_2CO_3, DMF, 75°C, 4 h, 95%. (b) $CHCl_3$, *t*-BuOK, THF/DMF, −78°C, 10 min, 72%. (c) i. HCO_2H, 115°C, 18 h; ii. $NaClO_2$, NH_2SO_3H, $MeOH/H_2O$, rt, 1.5 h, 72%. (d) i. CDI, THF, reflux, 1 h; ii. CH_3NO_2, *t*-BuOK, 0–5°C, 68%.[3] (e) Fe, HCl, EtOH, reflux, 20 h, 95%. (f) i. HCO_2NH_4, Pd/C, EtOH, 85°C, 18 h; ii. HCl, Et_2O, 0°C, 30 min, 99%. (g) $CH(OEt)_3$, DMSO, 65°C, 81%.

In summary, a new efficient method for the synthesis of 6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one has been developed that involves a new vicarious nucleophilic substitution reaction of nitroimidazole. The new method not only eliminates the hazardous gases used in the previous synthesis and is more efficient (30% versus 19% overall yield), but also uses less expensive starting material. Furthermore, it is expected that the new intermediates and improvements described here will find their way into the synthesis of other related compounds. The application of the new method in the preparation of biologically active compounds will be reported in due course.

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8. Palladium poisoning by residual sulfides in the deprotection of *N*-benzyl group following the literature procedure[1,3] was encountered in our hands, which forced us to pursue an alternative route to **1**.
9. Compound **4** has been previously prepared under acidic conditions, see: Rao, A. K. S. B.; Rao, C. G.; Singh, B. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2399.
10. All isolated products gave satisfactory spectroscopic and analytical data.
11. For an excellent reference on vicarious nucleophilic substitution reactions, see: Makosza, M.; Owczarczyk, *J. Org. Chem.* **1989**, *54*, 5094.
12. Preparation of **5**: To a stirred solution of *t*-BuOK (1.0 M in THF, 19.7 mL, 19.7 mmol) and anhydrous DMF (5 mL) at −78°C was added dropwise a mixture of 1-benzyl-5-nitroimidazole **4** (1.0 g, 4.92 mmol) and anhydrous $CHCl_3$ (646 mg, 5.41 mmol) in anhydrous DMF (3 mL) under nitrogen. After the addition was complete, the reaction was stirred at −78°C for 10 min and quenched by dropwise addition of a solution of AcOH (2.4 mL) in MeOH (5 mL). The resulting mixture was allowed to warm to room temperature, poured into ice-water and extracted with EtOAc. The EtOAc extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to give a gum. The crude product was passed through a silica gel pad (E. Merck, 230–400 mesh, 30 g), eluting with EtOAc/hexane (1:3) to give 1.0 g (72%) of 1-benzyl-4-dichloromethyl-5-nitro-imidazole **5** as an oil, ^1H NMR ($CDCl_3$) δ 5.60 (s, 2H), 7.26 (s, 1H), 7.35 (m, 2H), 7.44 (m, 3H), 8.01 (s, 1H).
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