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An Improved Process for the Preparation of Trimethylhydrazine and Its Coupling with an Activated Acid Intermediate

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Abstract:

Trimethylhydrazine (TMH) was prepared in two steps from 1,1-dimethylhydrazine, using an easy to scale-up procedure that avoided difficult acid−base extractions. The procedure provided TMH as a solution in 1,4-dioxane, in a form that was easy and safe to handle in a coupling with an enantiomerically pure, sterically hindered, Boc-protected-amino acid, 1. This key coupling reaction in the preparation of 3 was accomplished through the corresponding acid chloride, thereby avoiding the use of expensive coupling reagents.

Introduction

Trimethylhydrazine (TMH) is a ubiquitous component in the preparation of new chemical entities.[1] En route to obtaining multigram quantities of a new drug candidate possessing growth hormone releasing properties (**3**), the necessity for a safe and reliable process for the preparation of TMH on large scale became evident. Additionally, coupling TMH with sterically hindered acid **1** using an inexpensive coupling agent or, better yet, through a reactive intermediate of **1**, such as its acid chloride, was desired (Scheme 1).

Results and Discussion

Methods reported in the literature for the preparation of TMH include the reduction of methylene dimethylhydrazine using $LiAlH_4$ or catalytic hydrogenation[2,3] as well as the reduction of *N*-formyl dimethylhydrazine with $LiAlH_4$.[4] Usually, TMH was isolated as the HCl salt using acid−base extractions.

Reaction of 1,1-dimethylhydrazine with ethyl formate was executed easily on a 5-kg scale according to a procedure already described[4c] and yielded 1-formyl-2,2-dimethylhydrazine (**4**) in 89% yield (Scheme 2).

The reduction of **4** with $LiAlH_4$ was initially done in THF at room temperature. After an exothermic quench (external cooling at −35 °C was required to control the heat release) using ethylene glycol,[5] a thick, gummy mixture resulted that stuck to the stir shaft and further caused its destruction. Eventually, TMH (**5**) was obtained as a 5% w/w solution by co-distillation with THF,[6] requiring additional THF to be periodically added to distill all of the TMH out.

In an attempt to obtain a more concentrated solution of **5**, 1,4-dioxane was chosen as the reaction solvent. After the ethylene glycol quench, a gummy mixture resulted again, and TMH and 1,4-dioxane were co-distilled, resulting in four fractions, the first two of which contained TMH in higher concentration (13% w/w). The last fractions collected did not contain product, as monitored by ^1H NMR analysis.

Exothermicity of the ethylene glycol quench of excess $LiAlH_4$ required the use of a reactor at −35 °C (external temperature) while the mixture of TMH (plus cosolvent) had to be distilled at about 100 °C (internal temperature). Equipment restrictions meant that these operations had to be done in different reactors. Due to the thick slurry nature of the resulting mixture and stirring difficulties encountered during the quench, a transfer to a second container for distillation was impossible without the potential exposure of operating personnel to TMH.[7] These mechanical issues were circumvented by quenching the reaction with 1,2-propylene glycol, which resulted in a slurry that was easy to stir, both at room temperature and at 100 °C and which was transferred using vacuum to the distillation reactor. Thus, exposure of operating personnel to TMH was eliminated. Scale-up of the reaction to 2 kg was uneventful, and the mixture of product and 1,4-dioxane was distilled (92−96 °C). In this way, a less concentrated solution of TMH (7.4% w/w) was obtained, even when the overall yield remained unchanged (70%).[8] Performance of the TMH solution in 1,4-

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(5) For a discussion of the complexation on aluminum ions with polydentate ligands such as ethylene glycol, see: McMahon, C. N.; Alemany, L.; Callender, R. L.; Bott, S. G.; Barron, A. R. *Chem. Mater.* **1999**, *11*, 3181. Saraswathi, M.; Miller, J. M. *Can. J. Chem.* **1996**, *74*, 2221.

(6) The concentration of **5** in THF was determined by integration of the CH_3 signal in the ^1H NMR spectra.

(7) For information on the toxicity of TMH, see: Toth, B. *Cancer* **1977**, *40*, 2427. Nagel, D.; Toth, B.; Kupper, R.; Erickson, J. *J. Natl. Cancer Inst.* **1976**, *57*, 187.

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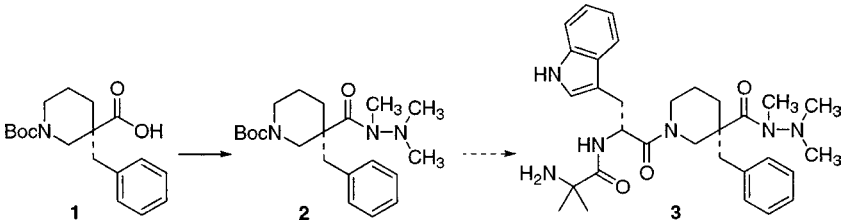
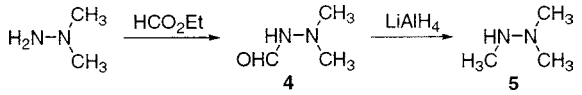
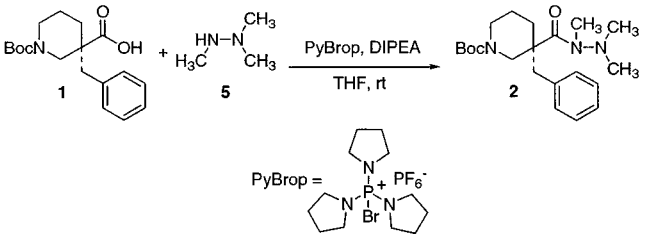
Scheme 1



Scheme 2



Scheme 3



dioxane in the preparation of **2** was comparable to that of the solution of TMH in THF.

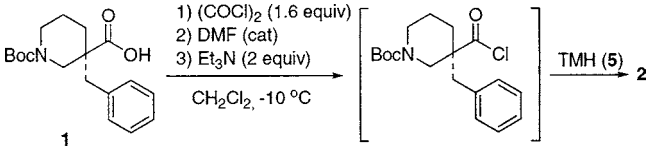
With a reliable procedure for the preparation of TMH in hand, we studied the coupling of TMH with **1**. Coupling of a 5% w/w solution of TMH in THF with **1** was initially done using PyBrop and DIPEA in THF at room temperature[9] (Scheme 3). Isolation of the resulting hydrazide from the reaction mixture was problematic due to the hygroscopic nature of the solid that was obtained under these conditions. Additionally, the DIPEA·HBr salt that contaminated the crude product caused problems in the subsequent step of the synthesis. Eventually, these conditions afforded hydrazide **2** in 65% yield along with recovered starting material (20%) after purification by column chromatography. Attempts to crystallize **2** from various solvent systems (CH_2Cl_2, EtOAc−hexanes, MTBE) to avoid purification by chromatography were unsuccessful. Several alternative conditions for the preparation of **2** using coupling agents were then investigated. The use of 1-propylphosphonic acid cyclic anhydride (PPACA, Et_3N, 0 °C, slow addition) or 1,1′-carbonyldiimidazole (CDI) resulted in the recovery of unreacted starting material, while the coupling mediated by EDCI·HCl and DMAP resulted in decomposition products. In accordance with HPLC analyses that showed the disappearance of starting material, we believe that in the above cases the reactive intermediate formed but the subsequent nucleophilic attack of TMH failed. A summary of the results is depicted in Table 1.

Dissatisfied with the coupling results this far, we decided to pursue coupling the acid chloride derived from acid **1**,

Table 1. **Coupling attempts of TMH with (*R*)-*N*-Boc-3-benzylnipecotic acid**

entry	coupling agent	base	solvent	conditions	yield (%)
1	PyBrop	DIPEA	THF	rt, 48 h	65
2	CDI	n/a	THF	rt, 12 h	**1**
3	EDCI·HCl	DMAP	CH_2Cl_2	0 °C→rt, 2 h	dec
4	PPACA	Et_3N	CH_2Cl_2	0 °C, 6 h	**1**

Scheme 4



even though its generation would be difficult by the instability of **1** to Boc-deprotection. Activation of the acid as its acid chloride (oxalyl chloride, catalytic DMF, Et_3N at −10 °C) and subsequent reaction with a 5% solution of TMH in THF or 1,4-dioxane afforded the resulting hydrazide, which was easily purified by passing the crude product through a silica plug. Yields were generally in the 82−90% range without any apparent removal of the Boc group. Interestingly, the order of addition of reagents proved crucial for the successful formation of the acid chloride in the coupling. When Et_3N was introduced prior to oxalyl chloride and DMF in the reaction pot, only **1** was recovered as well as traces of **2** and decomposition products.[10] This may be due to the fact that, while the acid readily reacts with oxalyl chloride to give the acid chloride which then reacts with TMH, its Et_3N salt reacts differently, leading to decomposition and, upon quenching, results in the recovery of **1**. In summary, a reproducible method for the reaction of a sterically hindered acid with a 5−7% w/w solution of TMH in THF or 1,4-dioxane by preformation of the acid chloride using oxalyl chloride, DMF, Et_3N at −10 °C was developed. The reaction was further scaled to 3 kg to provide **2** in 90% yield (93% AUC by HPLC) after silica-plug purification.

Experimental Section

Reagents that were commercially available were used without further purification. Nuclear magnetic resonance spectra were obtained on a Bruker AC 300 spectrometer at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR. Thin-layer chromatographic (TLC) analyses were performed using 10 cm × 20 cm Analtech Silica Gel GF plates (25 μm thick).

(8) The difference of boiling temperatures between TMH (bp 59−61 °C) and 1,4-dioxane (bp 100 °C) would allow obtaining higher concentrations of TMH provided a fractionating column was used.

(9) The choices of coupling agents were made on the basis of the reported effectiveness of phosphinic reagents in the coupling of hindered amino acids and on the fact that PyBrop had been employed in this coupling with moderate success. See: Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.

(10) Et_3N was introduced initially to avoid unnecessary exposure of the *N*-Boc group to acidic conditions. Formation of the acid chloride was monitored by HPLC analysis by derivatization as its methyl ester (by quenching in a 1:1:8 mixture of MeOH, Et_3N, and CH_2Cl_2).

The TLC plate was visualized by UV light (254 nm). HPLC analyses were performed on an Agilent 1100 liquid chromatograph with a variable-wavelength UV detector (YMC ODS-AQ S 5μ-120 Å, 150 mm × 4.6 mm, 5 μm, eluent: 50% H_2O (0.05% v/v TFA), 50% CH_3CN, flow 1.0 mL/min, λ = 215 nm, column temperature = rt, injection volume = 20 μL).

Preparation of 1-Formyl-2,2-dimethylhydrazine (4). To a 50-L jacketed reactor equipped with a temperature probe, reflux condenser, nitrogen sweep, and an overhead stirrer was charged 2,2-dimethylhydrazine (5.0 kg, 83 mol) followed by ethyl formate (5.1 kg, 69 mol). The resulting mixture was heated at 50 °C for 48 h and then cooled to 20−25 °C, transferred to a rotavap flask, and concentrated to a residue, which was crystallized from heptane (15 L). After filtration and drying the resulting solids under vacuum, 1-formyl-2,2-dimethylhydrazine[4c] was obtained (5.4 kg, 89% yield).

Preparation of Trimethylhydrazine (TMH, 5). To a three-neck round-bottom flask equipped with a mechanical stirrer under nitrogen was charged LAH (25.8 g, 0.68 mol) followed by 1,4-dioxane (750 mL). The slurry was stirred for 10 min, and a solution of 1-formyl-2,2-dimethylhydrazine (50 g, 0.58 mol) in 1,4-dioxane (500 mL) was added using an addition funnel while maintaining the internal temperature below 45 °C. The mixture was then warmed to 50 °C and stirred at this temperature for 5 h. After cooling to room temperature, propylene glycol (280 mL) was added over 20 min while maintaining the internal temperature below 40 °C. The product was then distilled as a solution in 1,4-dioxane, and four fractions were collected (T of distillate = 92−96 °C). The first two fractions contained trimethylhydrazine in 9% w/w according to ^{1}H NMR integration (275 g, 59% yield). The third fraction contained 3% w/w (188 g, 72% combined yield). ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6 H), 2.48 (s, 3 H).

Scale-Up of the Preparation of 5. To a 100-L jacketed reactor equipped with a temperature probe, reflux condenser, nitrogen sweep, and an overhead stirrer was charged 97% LAH in premeasured bags (1 kg, 26 mol) followed quickly by 1,4-dioxane (30 L) via a stainless steel nitrogen pressure can. A solution of *N*-formyl-dimethylhydrazine (2 kg, 23 mol) in 1,4-dioxane (20 L) was added to the slurry over 100 min while maintaining the internal temperature below 50 °C. The mixture was heated at 50 °C for 1.5 h. The reaction progress was monitored by TLC using 9:1:0.1 CH_2Cl_2:MeOH:28% aq NH_4OH with visualization by iodine stain. (R_f of *N*-formyl-dimethylhydrazine: 0.5, R_f of trimethylhydrazine: 0.4). After cooling the mixture to 20−25 °C, propylene glycol (11.2 L, 153 mol) was charged over 65 min while maintaining the internal temperature below 45 °C. The slurry was cooled to 20−25 °C overnight and then vacuum transferred to a 72-L, unjacketed reactor equipped with a heating mantle, temperature probe, Syltherm reflux condenser, Dean−Stark trap, nitrogen sweep, and a mechanical stirrer. The product was distilled from the slurry at 92−98 °C over 8.5 h. Two main fractions were collected and assayed by ^{1}H NMR. The first fraction was 10.5 L (7.4% TMH w/w, 0.78 kg, 48% yield), and the second was 12 L and used as is in the following step.

Preparation of *N*-Boc-3-Benzylnipecotic Acid Trimethyhydrazide (2). *(1) Formation of the Acid Chloride.* To a 72-L unjacketed reactor equipped with a temperature probe, reflux condenser, nitrogen sweep, cooling bath, and an overhead stirrer was charged *N*-Boc-3-benzylnipecotic acid **1** (3 kg, 9.4 mol) followed by dichloromethane (30 L). The solution was cooled to −15 to −10 °C, and oxalyl chloride (1.3 L, 15.2 mol) was added over 15 min while the internal temperature was maintained below −10 °C. DMF (300 mL) was then charged to the mixture over 20 min followed by Et_3N (2.66 L, 19 mol) over 1.75 h. The reaction mixture was stirred at −15 to −10 °C for 4.25 h until the conversion was complete.[10]

(2) Coupling Reaction. A solution of trimethylhydrazine in 1,4-dioxane (1.05 kg in 15 kg, 7% w/w, 14.1 mol) and Et_3N (2.66 L, 19 mol) was added to the reaction mixture over 2 h using a fluid-metering pump, maintaining the internal temperature between −15 to −20 °C. The reaction progress was monitored by HPLC analysis. The mixture was stirred overnight at −20 °C and then was quenched by the addition of water (20 L) and extracted with dichloromethane (15 L). The organic phase was concentrated to a residue, and after purification using a silica plug (CH_2Cl_2:MeOH:NH_4OH, 92:7:1), trimethylhydrazide **2** was obtained as an oil (3.2 kg, 90% yield, 93% AUC by HPLC). ^{1}H NMR (DMSO-d_6) δ 1.30−1.85 (m, 3 H), 1.35 (s, 9 H), 2.47 (s, 6 H), 2.80 (s, 3 H), 2.85−3.30 (masked, 3 H), 2.95 (d, J = 16 Hz, 1 H), 3.18 (d, J = 16 Hz, 1 H), 6.97 (m, 2H), 7.15 (m, 3H). ^{13}C NMR (DMSO-d_6) δ 21.4, 24.4, 28.3, 31.4, 37.4 (br), 43.6, 43.9, 47.0, 49.6, 78.6, 126.3, 128.4, 129.7, 138.3, 154.7, 174.4.

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