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Communications to the Editor

Acrylate as an Efficient Dimethylamine Trap for the Practical Synthesis of 1-*tert*-Butyl-4-piperidone via Transamination

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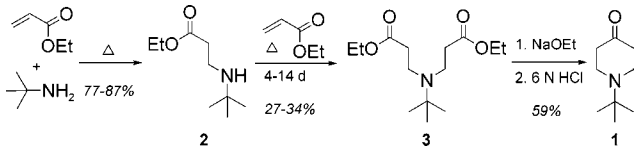
Abstract:

Efficient trapping of dimethylamine was the key to success in the transamination of 1,1-dimethyl-4-oxopiperidinium iodide with *tert*-butylamine to afford 1-*tert*-butylpiperidin-4-one in high yield. The use of sodium acrylate was found to provide an elegant way to both trap dimethylamine and provide a convenient method to allow purification in the subsequent extraction.

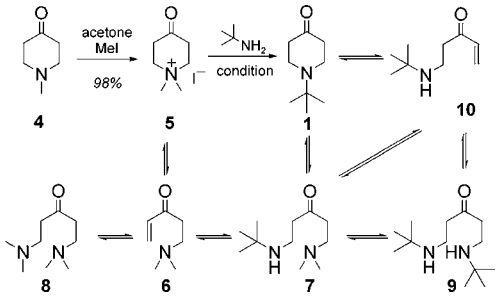
N-Substituted 4-piperidones are important synthetic building blocks to a considerable number of pharmacologically active agents. This pharmacophore is most notably prevalent in many CNS, antiallergic, and cardiovascular agents. In connection with our drug development program, we required kilogram quantities of 1-*tert*-butylpiperidin-4-one (**1**). The classical synthesis of **1** in 14−26% yield reported by Robinson[1] and Fankhauser[2] proceeded via a three-step sequence involving a bis-Michael addition of *tert*-butylamine with ethyl acrylate, followed by Dieckmann cyclization and saponification−decarboxylation (Scheme 1). Because of the steric hindrance of the *tert*-butyl group, the second Michael addition to generate **3** proceeded in only a 27−34% yield after heating at reflux for 4−14 days.

Scheme 1



An alternate approach to *N*-substituted piperidones developed by Mistryukov[3] and later modified by Kuehne[4] and others[5] has some advantages over the classical conditions. The troublesome bis-Michael addition is avoided, since the desired piperidine is prepared by an exchange reaction between 4-oxo-piperidinium iodide **5** and a primary amine (Scheme 2). However, the major shortcoming of this approach is that exchange reactions frequently do not go to completion due to unfavorable equilibria. Furthermore, hindered amines tended to produce bis-amine Michael adducts.

Scheme 2



Utilizing a modified procedure using toluene/water, K_2CO_3, and 10 equiv of *tert*-butylamine, the best assay yield by NMR of **1** from **5** was ∼70% as limited by the equilibria, which gave 40% isolated yield after distillation. Studies on solvent effects revealed that DMSO was effective in enhancing the reaction rate and shifting the equilibrium in favor of the desired product. Thus, the reaction in DMSO using excess *tert*-butylamine with distillation to remove dimethylamine gave a 95% assay yield and an 85% isolated yield on a 50 g scale, but on a 255 g scale the yield fell to 50%. We attributed this to the decreased efficiency in the evaporative removal of dimethylamine on scale-up due to reduced surface area relative to volume leading to longer reaction times. Addition of K_2CO_3 to the above reaction mixture afforded near quantitative yields on small scales but highly variable yields on larger scales. In these reactions run with K_2CO_3, we consistently observed significant amounts of solid deposited on the sides of the vessel above the reaction mixture as the reaction proceeded. By NMR examination, the solid was identified to be a dimethylamine derivative, most likely dimethylammonium carbonate/carbamate. Thus the formation of these materials physically removed dimethylamine from the reaction, and the reaction was driven forward to product. When the solid deposit was thrown back into the reaction mixture, we observed an immediate decrease of product **1** as monitored by real time FTIR analysis, supporting that dimethylamine has been reintroduced and

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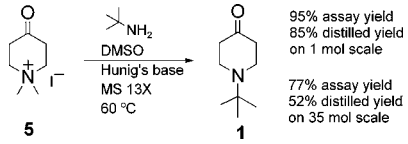
Scheme 3



promoting the equilibria in the reverse direction. Further studies on removal of dimethylamine by distillation and displacement with *tert*-butylamine were only marginally effective and required large amounts of *tert*-butylamine.

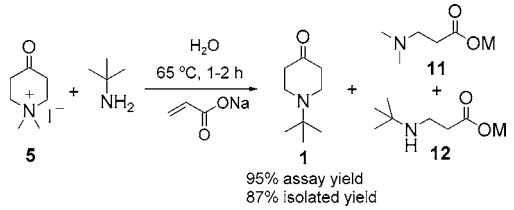
To gain further understanding, we studied the reaction by NMR and FTIR. Upon mixing of all reagents, all of salt **5** was consumed within 5 min with little product **1** formation. NMR analysis showed that the major product at this point was compound **7** and that no olefinic substances were present, as these must be highly reactive and short-lived. Therefore the key for successful reaction would be to selectively remove dimethylamine from the reaction. The studies also showed that rapid removal is also critical for high yields of **1**, since it is not completely stable under the reaction condition.

A number of solid-phase absorbents were screened for the ability to absorb dimethylamine, and 13X molecular sieves (8−12 mesh) were found to be the most effective. Reaction reflux liquors were allowed to pass through a bed of 13X sieves (2 mL sieves per gram of salt **5**) and returned to the reaction. The progress of the reaction was monitored by online FTIR and offline GC, and when the reaction rate slowed, the molecular sieves were replaced with fresh sieves. Using this setup, treatment of salt **5** (up to 1 mol scale) with excess *tert*-butylamine in DMSO and an equivalent of Hunig's base, the reaction was typically completed in 4−6 h with two changes of sieves to give an ∼95% assay yield (Scheme 3). However, on multi-kilogram scale, the physical dynamics of the system changed significantly due to decreased surface area relative to volume, and extended reaction time (>24 h) was required. The yield, as a consequence, dropped to ∼75% due to formation of polymers. These polymers had been previously observed in the distillation of the product.

This led us to explore dimethylamine traps that would react covalently. Acrylate esters, such as methyl- and *tert*-butyl acrylates and methyl crotonate, proved to be highly reactive traps for dimethylamine with good selectivity over *tert*-butylamine in the ratios of 4−15:1 with the more hindered acrylate achieving the better selectivity. In DMSO at 60 °C, reactions were typically complete within 2−3 h with a near quantitative yield of **1**. To facilitate the isolation of **1** and the removal of the acrylates and their amine adducts, the reaction mixture was subjected to aqueous NaOH or TFA to hydrolyze the methyl 3-alkylamino-propanoates or the *tert*-butyl esters, respectively. Product **1** could then be isolated by a simple acid−base extractive procedure, but significant yield erosion (60% isolated yield) was observed due to decomposition under the saponification conditions.

To avoid this hydrolytic workup, we explored the use of acrylic acid as the dimethylamine trap.[6] We were gratified

Scheme 4



to observe the facile nature of this reaction. Furthermore, water could be used in place of DMSO as the reaction solvent. Thus heating a solution of salt **5** with excess *tert*-butylamine in water in the presence of acrylic acid sodium salt (from 5 eq acrylic acid and 4.6 eq of 10 M NaOH) at 65 °C for 1−2 h gave a 95% GC assay yield of *N*-*tert*-butylpiperidone **1**. The byproducts 3-(dimethylamino)-butanoate **11** and 3-*tert*-butylamino-butanoate **12** salts remained in the water layer during the extraction of the product into ethyl acetate. Evaporation of the organic extracts afforded essentially pure **1** in 87% assay yield. This material was assayed by GC to have a purity of 99.7 area % and 96.5 wt % and was suitable for Ra−Ni reduction of the ketone without catalyst poisoning problems. If required, the ketone could be further purified by distillation under reduced pressure to afford material of >99.9% purity. This process was demonstrated on a half-mole scale with similar efficiency.[7] The facile nature of this method should allow scale-up without issues.

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(7) **Experimental Procedure (acrylate method):** To a solution of acrylic acid (176 g, 2.5 mol) in water (500 mL) was slowly added 10 N sodium hydroxide (230 mL, 2.3 mol). Then 1,1-dimethyl-4-oxopiperidinium iodide (**5**)[10] (128 g, 0.5 mol) and *tert*-butylamine (1000 mL) were added, and the resulting solution was heated at reflux (65 °C) for 90 min. The product formation was monitored by GC assay which typically peaked at 90 min. After completion of reaction the excess *tert*-butylamine was removed at 25 °C/40 Torr. The product is volatile, and thus excessive heating must be avoided. The mixture was then extracted with ethyl acetate (500 mL), and the aqueous was back-extracted twice with ethyl acetate (250 mL). The combined organic was washed twice with aq NaCl (200 mL) and concentrated in vacuo at 20 °C to give 70 g of **1** as an oil with a purity of 96.5 wt % and 99.7 area % by GC assay (87% assay yield). Analytically pure sample (99.94 GC%) was obtained by distillation (∼109 °C/∼50 Torr and ∼58 °C/∼1 Torr; lit.[1] bp 92−94 °C/9 mm): ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.76 (t, J = 6.1 Hz, 4 H), 2.29 (t, J = 6.1 Hz, 4 H), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 208.83, 53.48, 45.61, 41.67, 26.10. The HCl salt of **1** was prepared from 2-propanol: ^{1}H NMR (600.1 MHz, DMSO-d_6) δ 11.50 (br s, 1 H), 3.70−3.65 (m, 2 H), 3.44−3.37 (m, 2 H), 3.10 (ddd, J = 16.6, 12.8, 6.0 Hz, 2 H), 2.45−2.40 (m, 2 H), 1.41 (s, 9 H); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 203.24, 62.92, 44.33, 37.29, 24.05. **(Distillation method):** A mixture of 1,1-dimethyl-4-oxopiperidinium iodide (**5**) (51 g, 200 mmol), *tert*-butylamine (200 mL), K_2CO_3 powder (30 g, 217 mol), and DMSO (200 mL) was heated at reflux (65 °C) under a condenser (condenser temperature at 35−40 °C) for 4 h. Then the mixture was slowly distilled over 1 h while fresh *tert*-butylamine (100 mL) was slowly added. After cooling to 20 °C, added water (1 L) and extracted with MTBE (300 mL). The aqueous layer was back-extracted with MTBE (100 mL). The combined organic was washed with aq NaCl and concentrated to an oil. Distillation of the oil under reduced pressure (bp 110 °C/45 mm) afforded 27 g (86%) of **1**.

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(9) A possible mechanism for achieving substantial rate improvement by acrylic acid or their esters is the intermediacy of acrylate adducts of **7**. Requaternization of the dimethyamine on **7** would be expected to facilitate elimination and be kinetically favored over acrylate addition to the nitrogen bearing a *tert*-butyl group.

(10) Compound **5** was readily prepared from commercially available 1-methyl-4-piperidone and methyl iodide in acetone (15 mL/g) at 25−30 °C. After stirring for 2 h, product precipitated and was isolated by filtration in 98% yield.

Salts of 4-piperidones are known to form carbonyl hydrates in aqueous solution.[8] NMR studies of ketone **1** as the free base and the monohydrochloride salt in DMSO-d_6 showed that both species exist predominantly in the keto-form (>98%) with less than 2% as the hydrate of the carbonyl group even in the presence of residual water.

In conclusion, we have determined the key to successful preparation of *N*-*tert*-butylpiperidone **1** via transamination reaction of salt **5** was efficient removal of dimethylamine and have evaluated several removal methods. Methods involving physical means such as distillation and adsorption by solid absorbents worked well for small scale preparations but were not suitable for large scale. We discovered sodium acrylate, which reacted with dimethylamine covalently in water, to be the most efficient and practical trap for a scalable synthesis. This procedure produced product **1** in high yield and high purity, wherein purification by distillation was not necessary. The accelerated rate of reaction also prevented polymerization observed in other methods.[9]

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