Selective Monoalkylation of Ammonia: A High Throughput Synthesis of Primary Amines

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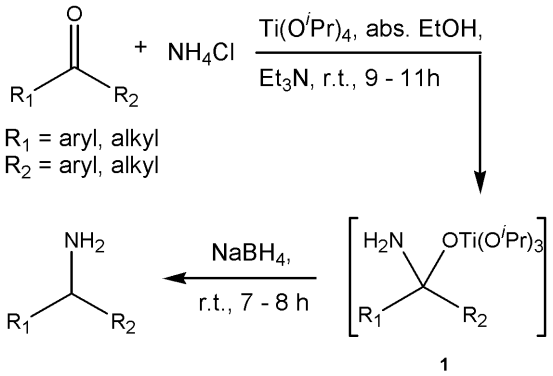
Abstract: Primary amines are obtained in good to excellent yields by highly selective monoalkylation of ammonia with alkyl and aryl ketones using titanium(IV) isopropoxide and sodium borohydride.

Key words: primary amines, reductive amination, titanium (IV) isopropoxide

The synthesis of amines and their derivatives has long been of interest because of their versatile utility[2] as medicinal agents and agrochemicals. The reductive amination of carbonyl compounds that allows an expedient access to diverse amines is one of the most widely applied reactions in synthetic organic chemistry.[3] The synthesis involves the formation of an imine or iminium intermediate upon exposure of a carbonyl compound to an amine followed by *in situ* reduction to an alkylated amine. Though many of the reported protocols for reductive amination reactions work well for the preparation of tertiary and secondary amines, synthesis of primary amines by reductive alkylation of ammonia is mostly compromised by over-alkylation[4] reactions. The formation of variable amounts of secondary and tertiary amines along with the desired primary amines is common. The synthesis of primary amines is, therefore, mostly addressed indirectly by using ammonia equivalents[5] such as tritylamine, diallylamine or allylamine. These protocols routinely require a subsequent deprotection step to get primary amines. Accordingly, development of a straightforward route for the synthesis of primary amines via selective monoalkylation of ammonia is an important objective.

In connection with our ongoing investigations on reductive amination reactions, we have recently used a combination of titanium(IV) isopropoxide and sodium borohydride in the reductive alkylations of primary and secondary amines.[6] Encouraged by our success, we envisaged that selective monoalkylation of ammonia with carbonyl compounds may be achieved with this one-pot reagent system.

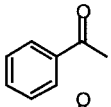
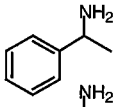
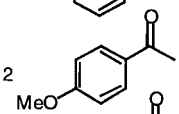
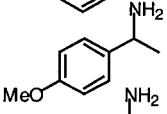
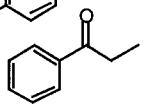
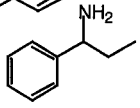
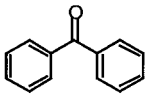
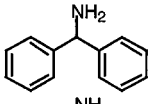
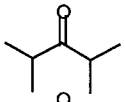
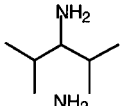
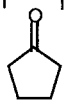
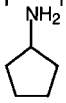
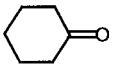
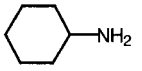
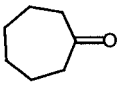
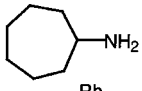
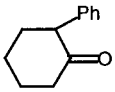
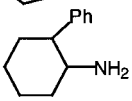
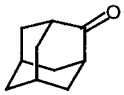
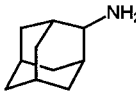
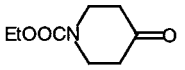
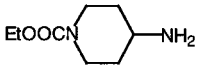
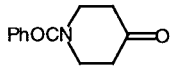
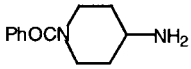
Indeed, this has been the case. We explored the application of this one-pot reagent system in the selective monoalkylation of ammonia with a variety of ketones to provide primary amines in good to excellent yields and the results are reported herein. A mixture of ammonium chloride and triethylamine has been employed as the ammonia equivalent; this requires no special handling techniques and alleviates the use of excess gaseous ammonia. In this reagent system, both alkyl and aryl ketones were converted to the desired primary amines in high yields; no over-alkylation of the product primary amines was observed. Titanium(IV) isopropoxide has been utilized[7] as a mild Lewis acid compatible with a variety of potentially acid-sensitive functional groups including acetals, acetonides, and silyl ethers. One of the traditional methods for carrying out reductive amination has been catalytic hydrogenation[3] which is, however, incompatible with a number of otherwise reducible functional groups such as nitro, cyano, and 'C-C' multiple bonds.



Scheme

The relevance of this protocol has been demonstrated on a structurally varied set of ketonic[8] substrates. The ketones were allowed to react with a mixture of ammonium chloride, triethylamine and titanium(IV) isopropoxide, followed by the treatment with sodium borohydride at room temperature. The results obtained for this representative group of ketones are summarized in the Table. The reaction may proceed through an intermediate aminocarbinolatotitanium(IV) complex **1** (Scheme),[6,7] which is either reduced directly or via equilibration of **1** to form a transient iminium species.[9] Typically, the intermediate complex **1** was first allowed to form by stirring a mixture of the ketone, ammonium chloride-triethylamine and titanium(IV) isopropoxide in absolute ethanol at ambient temperature for 9 -11 h. Sodium borohydride was then added and the resulting mixture was stirred for another 7-8 h at ambient temperature. Finally, the reaction mixture was quenched with aqueous ammonia (2 *M*) and then extracted with Et_2O. The product amines were isolated in their pure forms by simple extraction of the organic solution with hydrochloric acid (1 *M*), basification of the aqueous layer and subsequent extraction with Et_2O.

Table Reductive Amination of ketones[a,b]

entry	ketone	product	time,h[c]	yield,%[d]
1			10(7)	83
2			10(7)	82
3			10(7)	92
4			11(8)	73
5			11(8)	62
6			9(7)	70
7			9(7)	75
8			9(7)	73
9			11(8)	62
10			11(8)	78
11			11(7)	87
12			11(8)	77

[a] Molar ratio of ketone : NH_4Cl : NEt_3 : $Ti(O^iPr)_4$: $NaBH_4$ = 1 : 2 : 2 : 2 : 1.5. [b] ^1H and ^{13}C NMR and physical constant data were in complete agreement with the literature data or authentic samples. [c] The numbers in parentheses denote duration of reaction after $NaBH_4$ addition. [d] Yields are of isolated and purified products.

As shown in the Table, the ketones were converted to the corresponding primary amines in good yields. A comparison of the data in the Table shows little difference in the reactivity of the ketones towards reductive amination under the reaction conditions employed. Steric hindrance appeared to play only a limited role in dictating the outcome of the reactions in this series, with the only notable exceptions being entries 5 and 9. The reaction conditions were found to be tolerant to the substrates containing acid-sensitive carbamate (entry 11) and nucleophile/base-sensitive amide (entry 12) groups. Under these reaction conditions, only primary amines are formed – the traditional problem of over-alkylation of the product amines was not observed. The compatibility[6,7] of titanium(IV) isopropoxide with a variety of acid- or base-sensitive groups provides an additional advantage for targeting the syntheses of amines with reagent-sensitive motifs.

In conclusion, an efficient one-pot reagent system has been developed for the synthesis of primary amines by selective monoalkylation of ammonia with alkyl and aryl ketones using titanium(IV) isopropoxide and sodium borohydride. Because this method allows easy, direct access to diverse primary amines, it should find widespread application.

General Experimental Procedure. A mixture of the ketone (10 mmol), titanium(IV) isopropoxide (5.9 mL, 20 mmol), ammonium chloride (1.07 g, 20 mmol) and triethylamine (2.79 mL, 20 mmol) in absolute ethanol (20 mL) was stirred in a capped flask at ambient temperature for 9-11 h. Sodium borohydride (0.57 g, 15 mmol) and was then added and the resulting mixture was stirred for an additional 7-8 h at ambient temperature. The reaction was then quenched by pouring into aqueous ammonia (30 mL, 2 *M*), and the inorganic precipitate was filtered and washed with diethyl ether (50 mL). The organic layer was separated and the aqueous layer was extracted once with diethyl ether (50 mL). The combined organic extracts were next extracted with hydrochloric acid (20 mL x 2.1 *M*) to separate the non-basic materials. The acidic aqueous solution was washed once with diethyl ether (20 mL), then treated with aqueous sodium hydroxide (2 *M*) to pH 10-12, and extracted with diethyl ether (25 mL x 3). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and the solvent was removed to afford the primary amine in good to excellent yield. The products were typically more than 90% pure after work-up. Preparative TLC or column chromatography (CH_2Cl_2/MeOH, 9:1) was performed to obtain analytical samples. All products were identified by their spectral and analytical data.

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References and Notes

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