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A Versatile and One-Pot Strategy to Synthesize α-Amino Ketones from Benzylic Secondary Alcohols Using *N*-Bromosuccinimide

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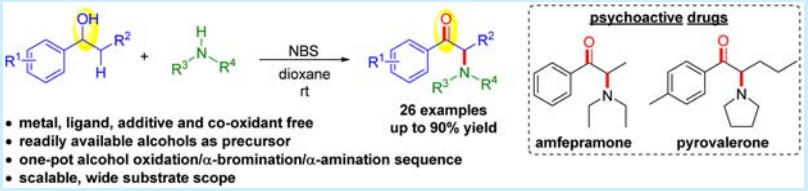
Supporting Information



ABSTRACT: A metal-free one-pot strategy has been developed for the first time to synthesize pharmaceutically important α-amino ketones from readily available benzylic secondary alcohols and amines using *N*-bromosuccinimide. This new reaction proceeds via three consecutive steps involving oxidation of alcohols, α-bromination of ketones, and nucleophilic substitution of α-bromo ketones to give α-amino ketones. Importantly, this novel one-pot greener reaction avoids direct usage of toxic and corrosive bromine. This methodology has been employed efficiently to synthesize pharmaceutically important amfepramone and pyrovalerone in a single step.

α-Amino ketones are important structural motifs existing widely in a large number of natural products and pharmaceuticals such as bupropion, pyrovalerone, *etc.* which are the potential pharmacotherapies for antidepressant and cocaine addiction (Figure 1).[1] Moreover, the substituted α-amino ketones display numerous biological applications.[2]

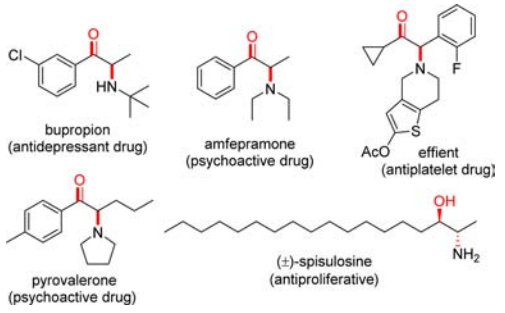
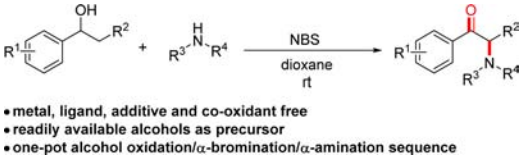


Figure 1. Representative examples for biologically significant α-amino ketones and alcohol.

The traditional methods to synthesize α-amino ketones start from ketones, which incorporate handling of toxic reagents such as bromine or a metal catalyst.[1c,3] Recently, MacMillan et al. displayed the synthesis of α-amino ketones from ketones through the direct coupling of α-carbonyls with an amine using a Cu catalyst.[4] Very recently, transition-metal-free oxidative α-C−H amination of ketone was reported by Guo using ammonium iodide as the catalyst and sodium percarbonate as a co-oxidant.[5] Despite the significant advances made from traditional approaches,[4−6] all of them were involved utilizing the ketones as a precursor and using metal or toxic reagents.[4−6] Consequently, the development of a novel protocol to synthesize these biologically relevant motifs from readily accessible starting material is always desired and challenging to the synthetic chemists. On the other hand, metal-free construction of C−C[7] and C−X[8] (X = N, O, S) bonds has emerged as a potential tool in organic synthesis. Particularly, C−N bond formation is very important in the synthesis of natural products[9] and pharmaceuticals. In this context, extensive effort has been made in recent years.[7a] However, there is still strong demand and the need for further exploration. Recently, we reported an efficient synthesis of isatins through C(sp^3)−H oxidation/intramolecular C−N bond formation of 2′-aminoacetophenones using a catalytic amount of iodine.[10] In continuation of our research toward metal-free synthetic transformations, herein, we disclose an elegant, greener, and one-pot protocol for the synthesis of α-amino ketones directly from easily available benzylic alcohols via sequential alcohol oxidation, α-bromination of ketone/C−N bond formation using readily available *N*-bromosuccinimide (NBS) (Scheme 1).

Scheme 1. α-Amino Ketones Synthesis from Benzylic Secondary Alcohols



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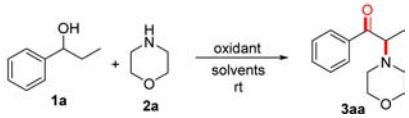
We initiated the optimization studies to synthesize α-amino ketones directly from benzylic secondary alcohols in a one-pot manner using 1-phenylpropan-1-ol **1a** as a model substrate.[11] The initial reaction was carried out by treating **1a** with 1.3 equiv of NBS in 2 mL of CH_3CN at ambient temperature for 24 h. To our delight, the desired product **3aa** was obtained in 75% yield (Table 1, entry 1). The other halogen sources such as NIS, NCS, I_2, and Br_2 were not effective for this one-pot synthesis (entries 2−5). The screening of different solvents was supportive for this transformation (entries 6−9), and a significant enhancement of the reaction yield (90%) was accomplished when 1,4-dioxane was used (entry 10). Other solvents afforded the desired compound in moderate yields (entries 11−13). When the reaction was performed under neat condition, the product **3aa** was obtained in 81% yield (entry 14).

Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant (1.3 equiv)	solvent	yield (%)[b]
1	NBS	CH_3CN	75
2	NIS	CH_3CN	12
3	NCS	CH_3CN	–
4	I_2	CH_3CN	–
5	Br_2	CH_3CN	–
6	NBS	THF	85
7	NBS	acetone	87
8	NBS	DMSO	68
9	NBS	DMF	80
10	**NBS**	**1,4-dioxane**	**90**
11	NBS	toluene	72
12	NBS	DCE	78
13	NBS	ethanol	77
14	NBS	neat	81

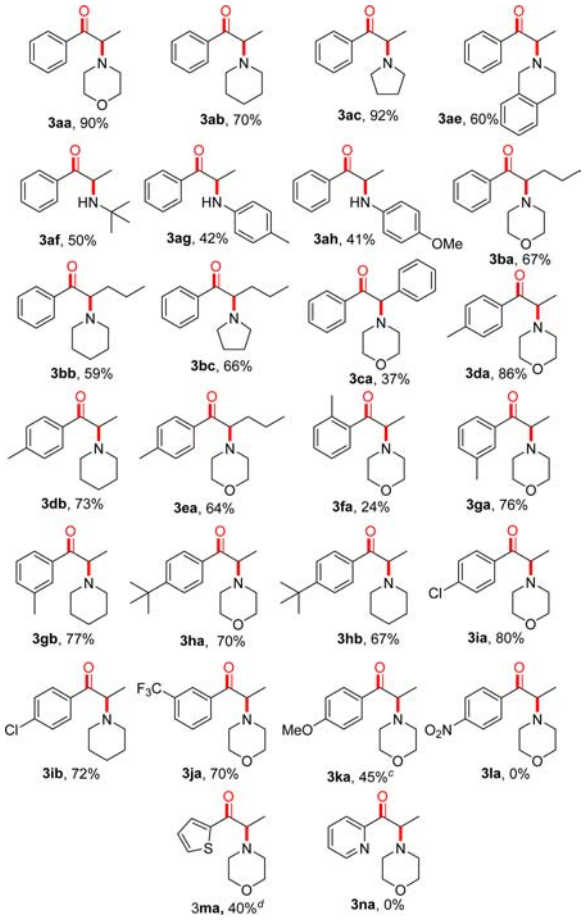
[a]All the reactions were carried out using **1a** (1.0 mmol) and **2a** (3 equiv) with 1.3 equiv of oxidant in 2 mL of solvent for 24 h. [b]Isolated yield.

The optimized reaction conditions revealed that α-amino ketones can be synthesized in excellent yield using 1.3 equiv of NBS in 1,4-dioxane at rt from benzylic secondary alcohols without using any metal, additives, additional oxidants, or peroxides. Having the optimized reactions in hand, the substrate scope was explored using different alcohols[12] and amines. In general, most of the benzylic secondary alcohols successfully provided the corresponding α-amino ketones in good to excellent yields, and the results are shown in Scheme 2. First, the reactions of model substrate **1a** with different amines such as piperidine, pyrrolidine, and 1,2,3,4-tetrahydroisoquinoline were investigated under optimized reaction conditions and the corresponding α-amino ketones were isolated in good to excellent yields (Scheme 2, entries **3ab**−**3ae**).

It is noteworthy to mention that aliphatic and aromatic primary amines such as *tert*-butylamine, *para*-toluidine, and *para*-anisidine were also well tolerated to produce the desired products in moderate yields probably due to lower nucleophilicity (entries **3af**−**3ah**). Substrates having an R^2 = *n*-Pr group also underwent reaction to deliver the desired products **3ba**−**3bc** in moderate to good yields. Similarly, the sterically hindered 1,2-diphenylethan-1-ol reacted with morpholine to afford **3ca** in a lower yield (37%). The methyl substitutions on the phenyl ring in various positions such as *ortho*/*meta*/*para* gave the corresponding products in 24−86% yield (entries **3da**−**3gb**). However, the compound **3fa** was obtained in poor yield, probably due to the steric hindrance of the *ortho* methyl group. The substrates equipped with the electron-releasing *tert*-butyl group at the *para* position underwent the conversion efficiently to give **3ha** and **3hb** in 70% and 67% yields, respectively. Notably, the alcohols with electron-withdrawing groups such as chloro and trifluoromethyl (CF_3) groups reacted very well to afford the desired products **3ia**−**3ja** in 71−80% yields. However, the substrate equipped with the electron releasing *p*-OMe group gave a 45% yield of desired product **3ka** in DMSO. Further, the scope of the reaction was extended to heterocyclic systems. Addition of 1 equiv of KI as additive was helpful to isolate 40% of α-amino ketone **3ma** having 2-thienyl group in CH_3CN. No product was observed in the case of substrates containing *p*-NO_2 or 2-pyridynyl groups, probably due to the electron-withdrawing effect (**3la** and **3na**).

This new reaction methodology was further successfully employed to synthesize psychoactive drugs amfepramone and pyrovalerone in one-pot synthesis from inexpensive materials using optimized reaction conditions to afford these bioactive derivatives in 60% and 68% yields respectively (Scheme 3).

Scheme 2. Substrate Scopes of α-Amino Ketones Synthesis[a,b]



[a]All the reactions were carried out using **1a**−**n** (1.0 mmol) and amine **2a**−**h** (3 equiv) with 1.3 equiv of NBS in 2 mL 1,4-dioxane for 24 h unless otherwise mentioned. [b] Isolated yields. [c] DMSO was used as solvent. [d] 1 equiv of KI was used as an additive.

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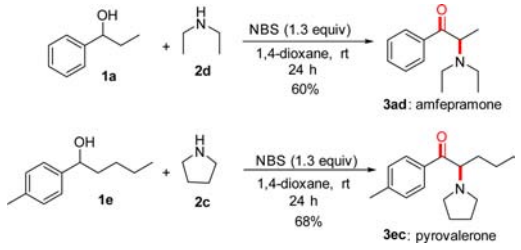
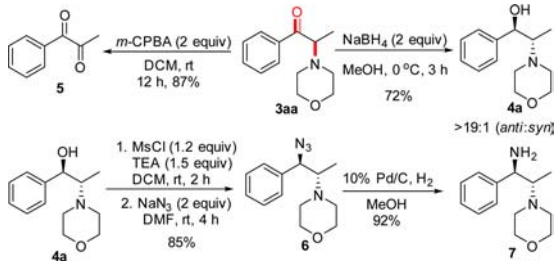
Scheme 3. One-Step Synthesis of Psychoactive Drug Amfepramone and Pyrovalerone



The synthetic application of α-amino ketone was demonstrated by their conversion to amino alcohol[13] derivatives through simple reduction using $NaBH_4$ in methanol to give *anti* amino alcohols **4a** (Scheme 4), whereas Pd/C yielded selectively

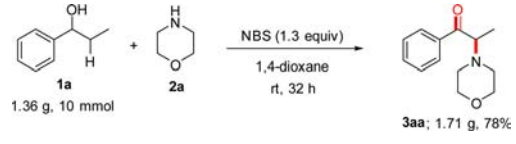
Scheme 4. Synthetic Transformations of α-Amino Ketone 3aa



syn diastereomer **4b** (6.7:1). Similarly, treatment of α-amino ketone with 2 equiv of *m*-CPBA provided diketone **5** in 87% yield via an iminium ion followed by hydrolysis.[14] In addition, the *anti* amino alcohol **4a** was further converted to azide derivative[15] **6** in 85% yield, which would be an important precursor for click reactions. The reaction proceeded in a stereospecific manner by displacement of the mesyl group through neighboring group participation[13c] of the morpholine nitrogen to give an aziridinium ion intermediate, with subsequent regiospecific ring opening at the benzylic position by azide to afford the product with retention of configuration. The hydrogenation of **6** gave 1,2-diamino derivative[16] **7** in 92% yield (Scheme 4).

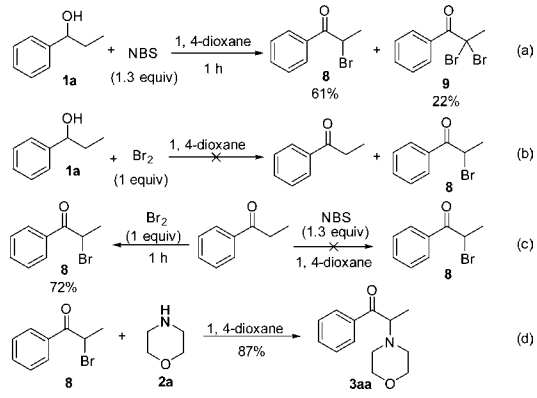
To show the consistency of this one-pot protocol, a gram scale experiment was performed by employing 1.36 g (10 mmol) of **1a** under the standard reaction conditions. This transformation proceeded smoothly to afford **3aa** in 78% yield (Scheme 5).

Scheme 5. Gram Scale Synthesis of α-Amino Ketone 3aa



To understand the reaction mechanism, the reaction of alcohol **1a** was carried out with *N*-bromosuccinimide in the absence of an amine. The reaction produced α-mono and dibromo ketones in 61% and 22% yield respectively (Scheme 6). This result clearly shows that the reaction proceeds through sequential alcohol oxidation and α-bromination of ketone. However, the reaction of alcohol **1a** with bromine did not provide any products. In addition, the reaction of propiophenone with *N*-bromosuccinimide and bromine was also investigated. We observed 2-bromo-1-phenylpropan-1-one **8** in 72% yield in the presence of bromine,

Scheme 6. Control Experiments



and no product was observed with NBS. These results clearly suggest that NBS is very crucial for the oxidation of alcohol to ketone and to generate bromine, which is further involved in the bromination of ketone (Scheme 6).

Further to confirm the reaction intermediacy, the progress of the reaction was monitored by ^{1}H NMR spectroscopy. The experiment results clearly reveal that the oxidation of alcohol is very fast and within a few minutes the alcohol is oxidized to ketone. The resulting ketone is further converted to α-bromo ketone by *in situ* generated Br_2. By comparison with authentic samples, the ^{1}H NMR signals of intermediates were assigned in Figure 2. For example, the triplet **a**′ and quartet **b**′ signals at 1.2

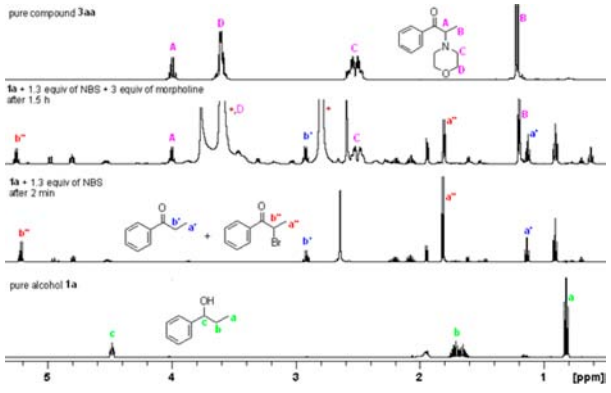


Figure 2. ^{1}H NMR experiments studies for the formation of α-amino ketone **3aa** in $CDCl_3$.

and 2.8 ppm belong to methyl (CH_3) and methylene (CH_2) groups of ketone, respectively. Further, the doublet **a**″ at 1.91 and quartet **b**″ at 5.29 ppm were assigned to α-bromo ketone. Next, the addition of 3 equiv of morpholine gives α-amino ketone by nucleophilic substitution of α-bromo ketone which is confirmed by the appearance of new peaks which include the doublet **B** at 1.26, the quartet **A** at 4.06, and multiplet peaks **C** and **D**. The addition of amines, at the appropriate time, to the reaction is very crucial and avoids the formation of α,α'-dibromo ketones. The addition of amines at a very early stage reduces the yield of product by quenching the *in situ* generated HBr.

On the basis of experimental results, NMR studies, and literature reports,[17] a possible reaction mechanism is depicted in Scheme 7. Initially NBS may react with alcohol **1a** to form hypobromite intermediate **1aa**, which will be further oxidized to give ketone and HBr. The oxidation is very fast and exothermic, and we believe that the heat generated in the reaction helps to

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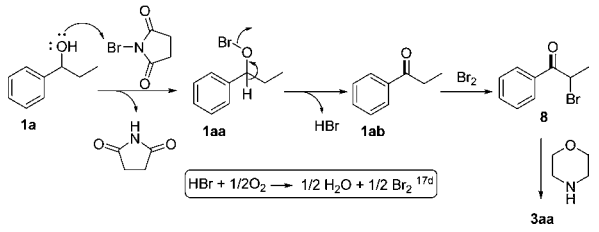
Scheme 7. Possible Reaction Mechanism



oxidize HBr in the presence of oxygen to give Br_2.[17d] Sequentially, the α-bromination of ketone **1ab** should occur by Br_2 generated *in situ*, and the nucleophilic substitution of α-bromo ketone with morpholine will produce α-amino ketone **3aa**. However, a detailed mechanistic study of this new one-pot synthesis and the asymmetric version of this methodology with organocatalysis is underway.

In summary, we have developed a novel approach to the synthesis of medicinally important α-amino ketones starting with readily available benzylic secondary alcohols using *N*-bromosuccinimide at ambient temperature without any additional oxidants. This reaction proceeds via three consecutive steps such as oxidation of alcohols, α-bromination of ketones, and nucleophilic substitution of α-bromo ketones to give α-amino ketones. Importantly, this novel one-pot reaction avoids direct usage of toxic and corrosive bromine as it is generated *in situ* in the reaction and be utilized. This methodology has delivered pharmaceutical agents such as amfepramone and pyrovalerone in good yields.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and copies of NMR spectra are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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