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N-Bromosuccinimide promoted and base switchable one pot synthesis of α-imido and α-amino ketones from styrenes†

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An *N*-Bromosuccinimide (NBS) promoted one pot strategy for the synthesis of α-amino functionalized aryl ketones starting from commercially available styrenes has been developed. NBS participates in multiple tasks, such as bromonium ion formation, oxidation of bromohydrin and providing a nucleophilic nitrogen source. The reaction can easily be switched between α-imido and α-amino ketones by the choice of base. This one pot strategy was successfully applied for the synthesis of psychoactive drug candidates, amfepramone, mephedrone and 4-MEC.

Carbonyl compounds with amino functionality at the α-position, such as α-amino and α-imido ketones, are an important class of motifs due to their presence in various biologically active natural and pharmaceutical compounds (Fig. 1).[1] These compounds are also important intermediates or precursors for the synthesis of biologically active chiral 2-amino alcohols[2] and different nitrogen containing heterocycles.[3]

Traditional methods to construct α-amino functionalized carbonyls require handling of lachrymatic phenacyl halides or toxic bromine to start from ketones.[1b,h,2d,i,4] Recent approaches to α-amino functionalized carbonyls by metal assistance include the rhodium catalyzed degradation of *N*-sulfonyl-1,2,3-triazole *via* rhodium carbenoid formation,[5] the Au/Ag catalyzed addition of alcohols to ynimides[6] and the α-amination of carbonyls using copper as a catalyst under air as an oxidant[7a] as well as using *N*-chloramine/Fe^{2+}/olefin.[7b] Metal free synthetic approaches include α-amination of ketones using ammonium iodide/sodium percarbonate,[8] NIS/TBHP,[9] and NBS/DBU,[10] and an NBS catalyzed one pot synthesis from benzylic secondary alcohols.[11] Due to the importance of α-amino functionalized carbonyls, herein we report an NBS promoted one pot strategy for the synthesis of α-amino functionalized carbonyls starting from readily available styrene.

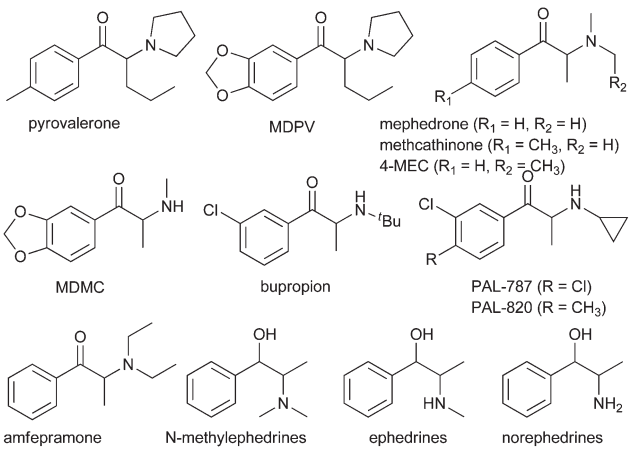

Fig. 1 Biologically important α-amino functionalized ketones and alcohols.

The method can be easily switched between α-amino and α-imido ketones by the choice of base.

NBS has versatile applications in organic chemistry, such as being a non-toxic cationic and radical bromine source as well as an oxidant.[12] Keeping this in mind, we planned to trigger and take advantage of various functions of NBS for the one pot synthesis of α-amino functionalized carbonyls from alkenes. Optimization was performed on simple styrene (**1a**) (Table 1). Reaction of styrene (**1a**, 1.0 equiv.) with NBS (2.0 equiv.) in H_2O : dioxane at 80 °C for 3 h followed by the addition of K_2CO_3 and stirring at room temperature for 12 h gave the α-imido ketone (**2a**) in 32% yield (Table 1, entry 1).[13]

The addition of NBS in two portions did not improve the yield (entry 2). When the reaction was carried out using H_2O as the solvent, **2a** was isolated in 30% yield (entry 3). Hence, it was decided to add an organic solvent as a co-solvent before the addition of the base. Dioxane was added to the reaction after 1.2 h, which was followed by the addition of K_2CO_3 and stirring at room temperature for 12 h to give **2a** in 55% yield (entry 4). When acetonitrile was used, **2a** was obtained in 51%

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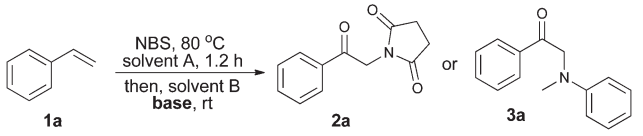
Table 1 Optimization of the reaction conditions[a]



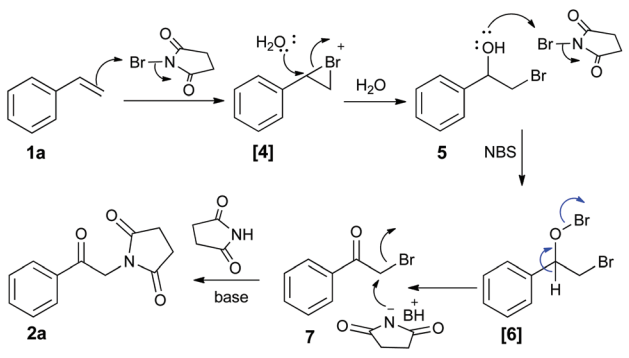
Entry	Solvent **A**	Solvent **B**	Base[d,e]	**2a**[b] (%)	**3a**[b] (%)
1	H_2O : dioxane	—	K_2CO_3	32	—
2[c]	H_2O : dioxane	—	K_2CO_3	33	—
3	H_2O	—	K_2CO_3	30	—
4	H_2O	Dioxane	K_2CO_3	55	—
5	H_2O	MeCN	K_2CO_3	51	—
6	H_2O	Acetone	K_2CO_3	57	—
7	H_2O	Acetone	$NaHCO_3$	40	—
8	H_2O	Acetone	LiOH	46	—
9	H_2O	Acetone	NaOH	48	—
10	H_2O	Acetone	Et_3N	38	—
11	H_2O	Acetone	DBU	67	—
12	H_2O	Acetone	MeNHPh[f]	—	72
13[g]	H_2O	Acetone	DBU	34	—
14[h]	H_2O	Acetone	DBU	—	—
15[i]	H_2O	Acetone	DBU	—	—

[a] Conditions: **1a** (1.0 mmol), NBS (2.0 mmol), solvent **A** (1 mL), 80 °C, 1.2 h then solvent **B** (2 mL), base (3.0 mmol), rt, 45 min. rt, 12 h. [b] Isolated yield. [c] NBS was added in two portions with a 30 min interval. [d] Reaction mixture was stirred for 12 h at rt after the addition of the inorganic bases. [e] Reaction mixture was stirred for 45 min at rt after the addition of Et_3N or DBU. [f] Reaction mixture was stirred for 6 h at rt after the addition of MeNHPh. [g] NIS was used as an NBS substitute. [h] NCS was used as an NBS substitute. [i] NCP was used as an NBS substitute.

yield (entry 5), whereas in acetone, **2a** was obtained in 57% yield (entry 6). Replacement of K_2CO_3 with the weak base $NaHCO_3$ as well as the stronger bases LiOH and NaOH did not improve the yield (entries 7–9). As expected, when the inorganic base was replaced with organic base Et_3N, nucleophilic displacement was completed in only 1 h at room temperature to give **2a** in 38% yield (entry 10). The use of the strong base DBU yielded **2a** in 67% yield in only 45 min (entry 11).

The reaction pathway includes the NBS mediated formation of a bromonium ion (**4**) followed by regioselective addition of water to give the bromohydrin (**5**) (Scheme 1).[14] The bromohydrin (**5**) may further react with NBS to form a hypobromite intermediate (**6**), which cleaves to form phenacyl bromide (**7**). Phenacyl bromide (**7**), upon base induced nucleophilic displacement with a succinimide anion, gives the α-imido ketone (**2a**).[10,15] Surprisingly, when *N*-methyl aniline was used as the base, α-amino ketone **3a** was isolated in good yield (entry 12) instead of the α-imido ketone **2a**. This is probably because of the less basic and more nucleophilic nature of *N*-methyl aniline, which undergoes direct nucleophilic displacement with *in situ* formed phenacyl bromide (**7**). The efficiency of other *N*-haloimides, such as NIS, NCS and NCP (*N*-chlorophthalimide), were also checked (entries 13–15) but only NIS gave the desired product in 34% yield.

With the optimization results in hand, we sought to explore the substrate scope for α-imido and α-amino ketones. Reaction of NBS with styrenes containing electron withdrawing groups, such as halides and $-NO_2$ (**1b–e**), afforded corresponding α-imido ketones (**2b–e**) smoothly after treatment with DBU in good yields (60–73%) (Fig. 2). Styrenes with electron releasing groups, such as 4-methyl and 4-*tert*-butyl, also afforded the corresponding α-imido ketones (**2f**, **g**) in good to moderate yields (65/70%). Styrene with strong electron releasing groups, such as the –OMe group, afforded unassignable complex reaction mixtures. β-Methyl styrene needs a longer heating time (7 h) to afford the corresponding α-imido ketones (**2i**) in moderate yield (56%). To our surprise, *trans*-stilbene did not give the corresponding α-imido ketone (**2j**). After forming these α-imido ketones by reacting styrenes with NBS, other *N*-bromoimides, such as *N*-bromophthalimide, *N*-bromosaccharin and 1,3-dibromo-5,5-dimethylhydantoin, were also examined.



Scheme 1 Possible reaction pathway.

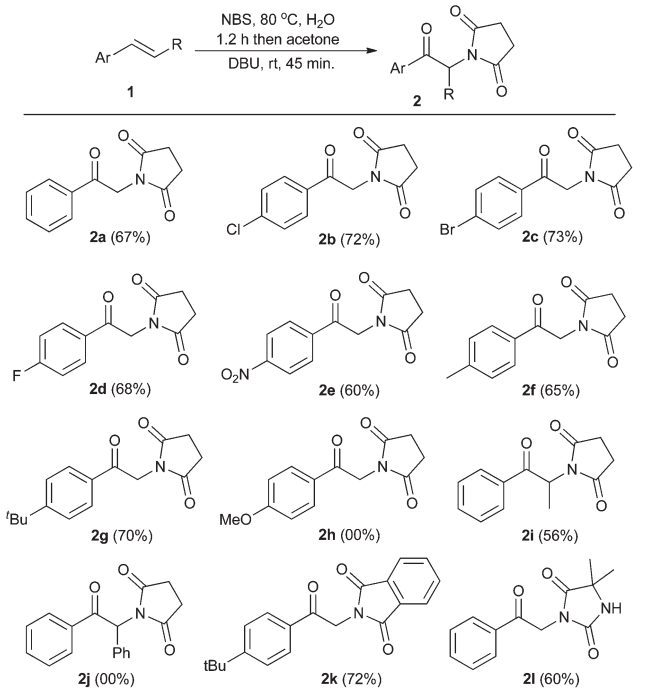


Fig. 2 Substrate scope for the synthesis of α-imido ketones.

Reaction of *N*-bromophthalimide with 4-*tert*-butyl-styrene provided the isoindole-1,3-dione derivative (**2k**) in 72% yield. *N*-Bromosaccharin and styrene (**2a**) under optimized condition afforded only phenacyl bromide (**7**), which might be because of the lower nucleophilicity of the nitrogen anion of the corresponding imide due to the presence of the adjacent sulfone group making it more stable. 1,3-Dibromo-5,5-dimethyl-hydantoin gave the corresponding α-imido ketone (**2l**) in moderate yield (60%). Aliphatic alkenes as well as 2-vinylpyridine produce complex reaction mixtures, which might be due to low selectivity.

Next, encouraged by having α-imido ketones, we turned our attention towards investigating the scope of α-amino ketones using various amines. Treatment of various styrenes with NBS followed by the addition of *N*-methyl aniline gave α-amino ketones (**3a–f**) in moderate yields (48–69%) (Fig. 3). *N*-Ethyl aniline was also examined with styrene (**1a**) and 4-*tert*-butyl-styrene, which gave the corresponding α-amino ketones (**3g**, **h**) in good yields (61/65%). When *N*,*N*-diphenyl-amine was treated with styrene (**1a**), only unreacted phenacyl bromide (**7**) was recovered.[16] Styrene (**1a**) was treated with NBS/4-methyl-aniline to give the α-amino ketone (**3i**) in 61% yield. As expected, β-methyl styrene required a longer time to give the corresponding α-aminated ketones in good yields. β-Methyl styrene was treated with NBS followed by 4-methoxy-aniline and 4-methyl-aniline to give the corresponding α-anilated ketones **3j** and **3k** in 79% and 83% yields, respectively. After successful treatment of the styrenes with anilines and *N*-alkyl anilines, we decided to explore the scope of more reactive alkyl amines. When β-methyl styrene was treated with NBS followed by morpholine, it produced α-amino ketone (**3l**) in good yield (78%). Other cyclic amines, such as piperidine and pyrrolidine, afforded the corresponding α-amino ketones (**3m**, **n**) in 62% and 65% yields, respectively. β-Methyl styrene upon treatment with NBS/tetrahydroisoquinoline afforded α-amino ketone (**3o**) in reasonable yield (70%). This strategy was also applied for the one pot synthesis of amfepramone (**3p**), mephedrone (**3q**) and 4-MEC (**3r**). Reaction of β-methyl styrene with NBS followed by diethylamine provided amfepramone (**3o**) in one pot (62%). Mephedrone (**3q**) and 4-MEC (**3r**) were isolated in 61% and 65% yields after treatment of β-methyl styrene with NBS followed by dimethylamine and *N*-ethyl-methylamine, respectively.

In conclusion, we have disclosed an efficient protocol for the one pot synthesis of α-amino functionalized aryl ketones mediated by NBS from commercially available styrenes. NBS has multiple functions in the reaction course, such as bromohydrin formation *via* bromonium ion formation of the C=C double bond, oxidation of bromohydrin and providing a nucleophilic nitrogen source. The reaction path could be easily switched between α-imido and α-amino ketones by simply changing the base. The efficacy of the strategy was checked by the one pot synthesis of amfepramone, mephedrone and 4-MEC. Further exploration of various nucleophiles and application of this strategy in the synthesis of bioactive natural products is ongoing in our laboratory.

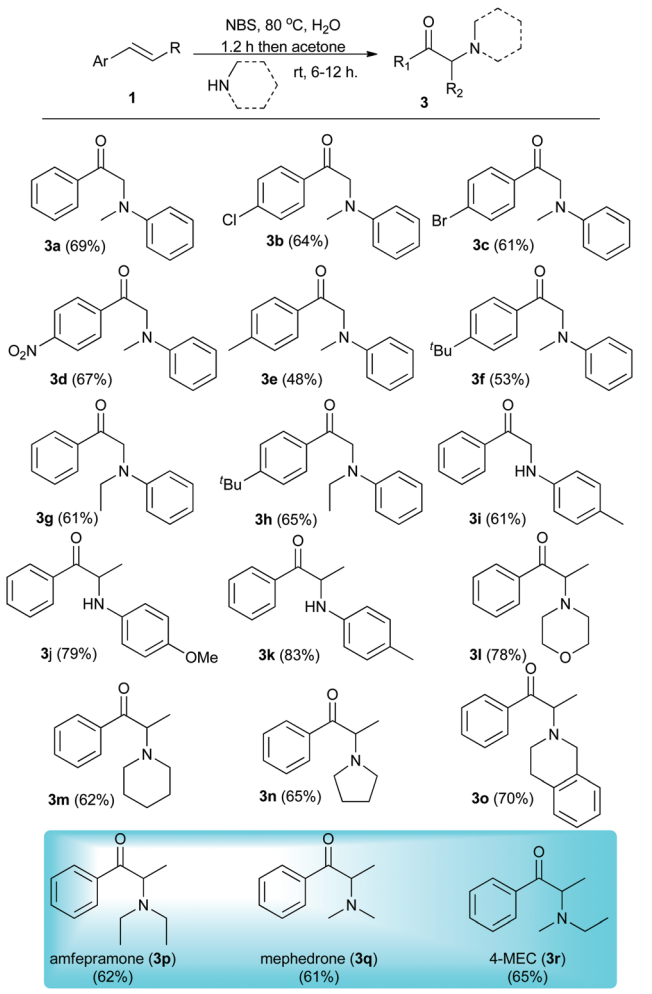


Fig. 3 Substrate scope for the synthesis of α-amino ketones.

Acknowledgements

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14 Styrene (**1a**) upon stirring with 1.0 equiv. of NBS at room temperature in water for 30 min gave bromohydrin (**5**) in 89% yield, which, upon heating with 1.0 equiv. of NBS at 80 °C for 2 h, gave phenacyl bromide (**7**) in 83% yield. When styrene (**1a**) was heated with 2.0 equiv. of NBS in water for 2 h, it furnished the phenacyl bromide (**7**) in 80% yield.

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