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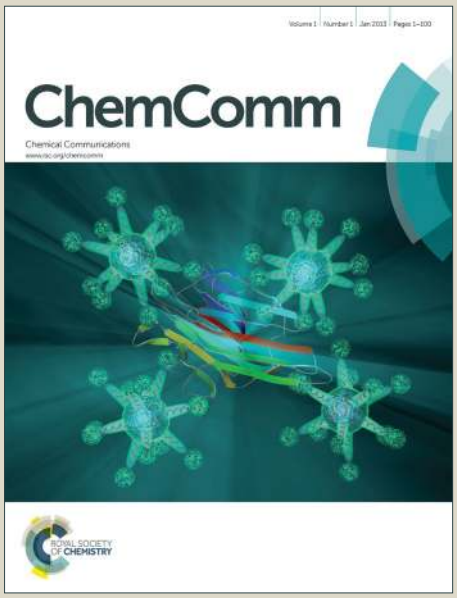

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Iodine(III) Mediated Oxidative Rearrangement of Enamines: Efficient Synthesis of α-Amino Ketones

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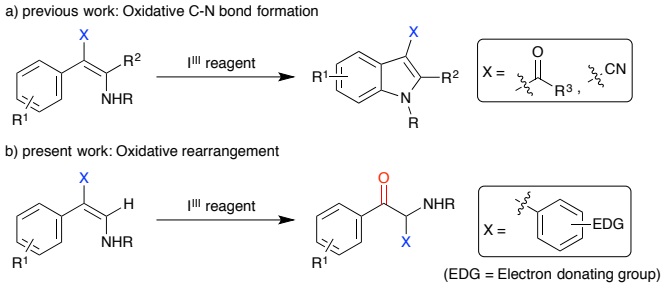
An iodine(III)-mediated, group-selective oxidative rearrangement of β,β-diarylenamines to α-amino ketones has been accomplished with excellent yield. The developed reaction involves the initial oxidation of enamine to α-acyloxyimine intermediate and concomitant semipinacol rearrangement.

Hypervalent iodine compounds, both iodine(III) and iodine(V) species, have been established as highly valuable reagents in organic synthesis.[1] These reagents are mainly employed as mild and environmentally benign oxidizing reagents that replace the use of toxic heavy metal oxidants.[2] In addition to the simple oxidation,[3] α-functionalization of carbonyl compounds,[4] cyclization,[5] atom-transfer[6] and oxidative rearrangements[7] were also successfully accomplished using iodine(III) reagents. Among them, cyclization through C-heteroatom bond formation is well documented for the synthesis of various heterocyclic compounds.[5] A representative example includes the synthesis of indole derivatives from electron deficient enamines *via* iodine(III) mediated C-N bond formation (Scheme 1a).[8] In contrast, cyclization of electron rich enamines did not afford the expected indole derivative; instead an unusual oxidative rearrangement[9] to α-amino ketones was observed, which is the subject of this communication (Scheme 1b).



Scheme 1. Reaction of substituted enamine with hypervalent iodine reagent.

α-Amino ketone motifs are frequently encountered as an integral part of many pharmaceutically important molecules and natural products.[10] They exhibit a wide range of biological activities, such as anti-depressant, appetite suppressant, and anti-platelet properties. Some of the representative examples are shown in Figure 1. Most of the strategies developed to date for the synthesis of α-amino ketones utilize either metal catalysed[11] or metal free[12] amination of ketone or its derivatives. However, development of new strategies for the synthesis of these biologically important scaffolds from complementary substrates[12a, 13] is in high demand. Herein, we reveal an efficient chemoselective oxidative rearrangement of enamines for the synthesis of α-amino ketones.

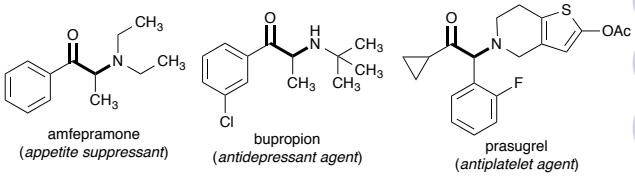
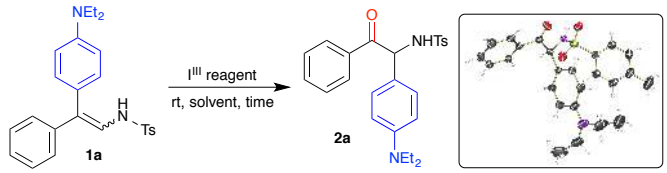


Figure 1. Examples of therapeutically important α-amino ketones.

At the outset, we synthesized β,β-diarylenamine **1a** as model substrate from 1,2,3-triazole and *N*,*N*-diethylaniline under rhodium catalysis.[14] Reaction of equimolar mixture of **1a** and [bis(trifluoroacetoxy)iodo]benzene (PIFA) in dichloromethane (DCM) afforded **2a** in 61% yield through oxidative rearrangement, with a remarkable reaction time of 5 min (Table 1, entry 1). The structure of α-amino ketone **2a** was unambiguously confirmed by X-ray analysis (Table 1). Further to improve the yield, various solvents were screened, such as toluene, tetrahydrofuran (THF) and chloroform. All of them gave the product **2a** with decrease in yield (Table 1, entries 2-4). Next, increasing the equivalents of PIFA to 1.2 in DCM furnished the α-amino ketone **2a** in 81% yield (Table 1, entry 5). No improvement in yield of **2a** was observed with portionwise addition of PIFA over 5 min interval. Changing PIFA to diacetoxyiodobenzene (PIDA) and diphenyliodonium triflate gave inferior results compared to PIFA, even after prolonged reaction time (Table 1, entries 6-7).

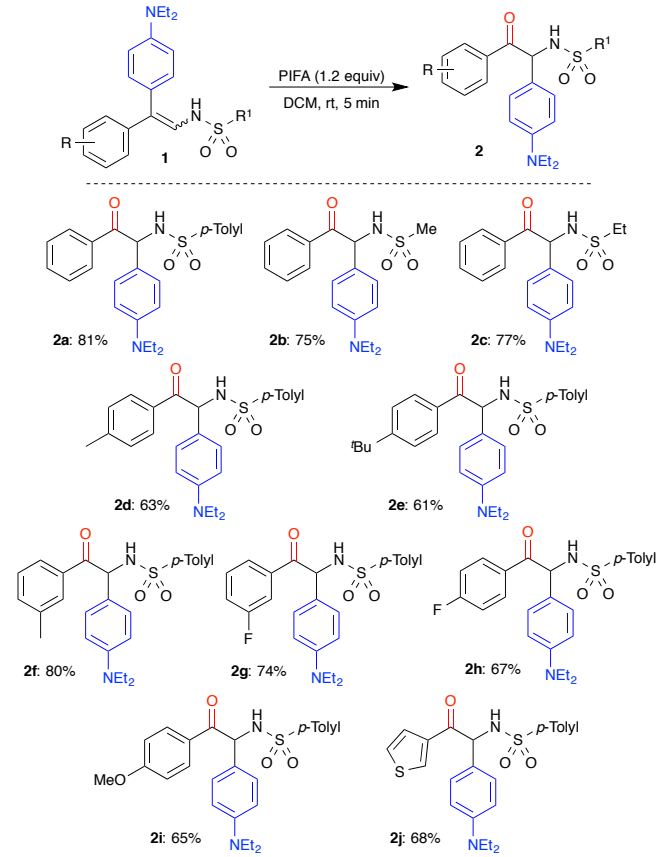
Table 1. Oxidative rearrangement of enamines: Optimization.[a]



Entry	I^{III} reagent (X equiv)	Solvent	Time	Yield (%)[b]
1	PIFA (1)	DCM	5 min	61
2	PIFA (1)	Toluene	5 min	40
3	PIFA (1)	THF	5 min	42
4	PIFA (1)	$CHCl_3$	5 min	39
5	PIFA (1.2)	DCM	5 min	81 (76)[c]
6	PIDA (1.2)	DCM	0.5 h	26
7	Ph_2IOTf (1.2)	DCM	48 h	20

[a] enamine **1a** (0.12 mmol, 1 equiv), I^{III} reagent (X equiv), solvent (1 mL), rt; [b] All are isolated yield; [c] 20 min and portionwise addition of PIFA.

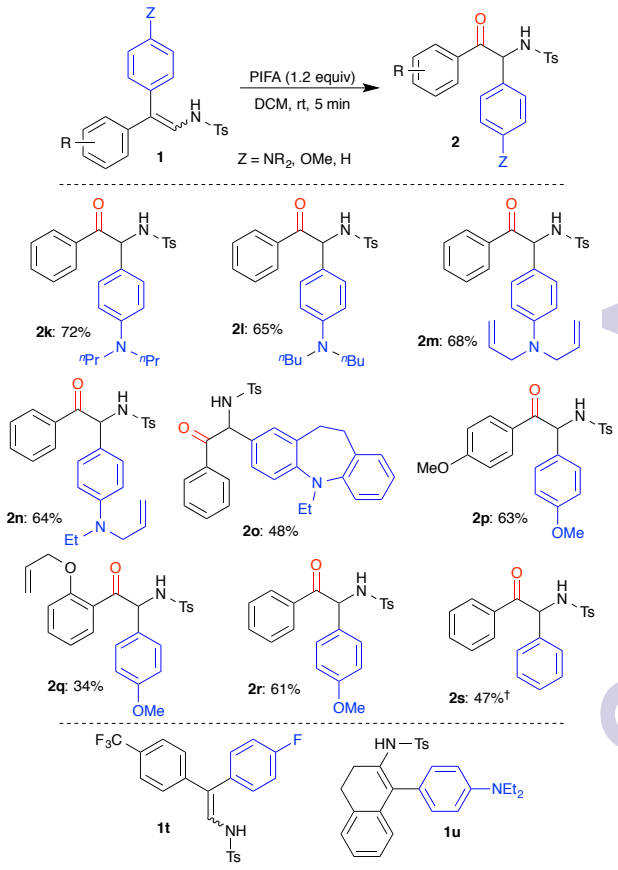
Having shown an efficient oxidative rearrangement of enamine **1a** to *α*-amino ketone **2a**, we were interested in exploring the generality of the reaction with respect to various substitutions on nitrogen and one of the aryl groups. As shown in Scheme 2, reaction of enamines having tosyl, mesyl and ethanesulfonyl substitutions on the nitrogen group gave the corresponding *α*-amino ketones (**2a**-**2c**) in 81, 75 and 77% yield, respectively. Reaction also tolerates diverse substitution such as 4-methyl, 4-*tert*-butyl, 3-methyl and 3-fluoro on the aromatic ring and led to the synthesis of corresponding *α*-amino ketones (**2d**, **2e**, **2f** and **2g**) through chemoselective oxidative rearrangement of the electron-rich aryl group.



Scheme 2. Synthesis of *α*-amino ketones.

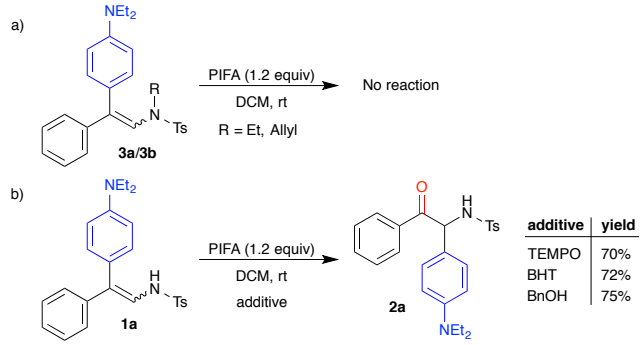
Similar chemoselectivity for the electron rich arene was observed with enamine **1h**, which has electronically differe t aryl groups, (4-fluorophenyl and 4-(*N*,*N*-diethylamino)phenyl. More interestingly, a competition between 4-anisyl and 4-(*N*,*N*-diethylamino)phenyl substituents also afforded product **2** where 4-(*N*,*N*-diethylamino)phenyl group selectively underwent the migration. Furthermore, heteroaryl, thiophen-2-yl substituted *α*-amino ketone **2j** was also synthesized in 68% yield from corresponding enamine.

Consequently, we studied the effect of the electronic nature of the substitutions in the oxidative rearrangement (Scheme 3). In all the cases we have examined, the more electron rich aryl moiety (a symmetrically and unsymmetrically-substituted 4-(*N*,*N*-dialkylamino)phenyl group) selectively migrated to afford *α*-amino ketones (**2k**-**2n**) in good yield. Presence of alkene functionality in the substrates was well tolerated under the optimized conditions to afford the corresponding products **2l** and **2n** in ~68% yield. Iminodibenzyl, an electron rich heteroarene substituted enamine furnished the *α*-amino ketone **2o** in 48% yield. Similar to aniline based enamines, anisole based enamine derivatives also selectively underwent oxidative rearrangement to give products **2p**, **2q** and **2r** in moderate to good yield. Interestingly, oxidative rearrangement of electronically neutral *β*,*β*-diphenylenamine **1s** was sluggish and on prolonged reaction time (12 h) gave the product **2s** in 47% yield. However, the electron poor enamine **1t** and the disubstituted enamine **1u** did not furnish the expected rearrangement products. Instead, oxidative cleavage to the ketone and decomposition of the enamine were observed, respectively (see supporting information).



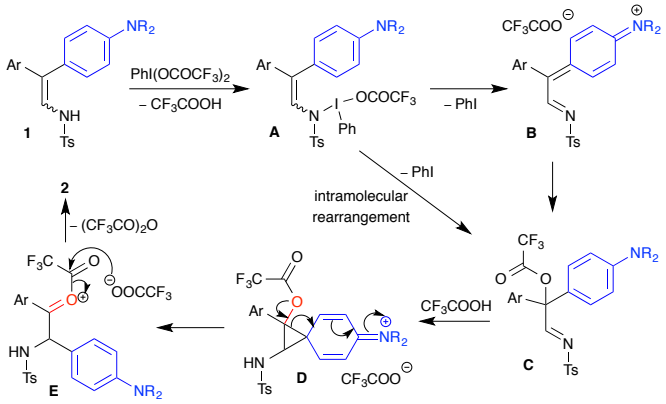
Scheme 3. Synthesis of functionalized *α*-amino ketones. † 12 h

After the successful identification and demonstration of unusual oxidative rearrangement of *β,β*-diarylenamine **1**, we were interested in probing its possible mechanism. Initially, we studied the role of the free NH in the enamine. Unsuccessful rearrangement of *N,N*-disubstituted enamines **3a**/**3b** under the optimized reaction conditions revealed the critical nature of a free 'NH' group in oxidative rearrangement of enamine (Scheme 4a). Subsequently, we performed the oxidative rearrangement of enamine **1a** in the presence of radical scavengers like TEMPO, BHT and BnOH. In all the three reactions, the product **2a** was isolated in excellent yield, which rules out the formation of radicals and favors the ionic pathway (Scheme 4b).



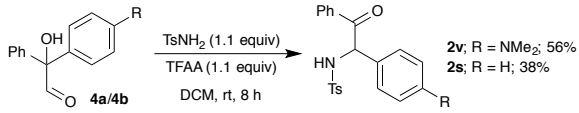
Scheme 4. a) Oxidative rearrangement of *N,N*-disubstituted enamines; b) oxidative rearrangement of enamine **1a** in presence of radical scavengers.

Based on these studies, we proposed a plausible mechanism for the oxidative rearrangement of *β,β*-diarylenamine **1** (Scheme 5). The reaction of **1** with $PhI(OCOCF_3)_2$ (PIFA) would give the iodonium intermediate **A** through substitution of 'CF_3COO-' with enamine **1**. Next, enamine assisted reduction of iodonium **A** to phenyl iodide and cationic imine **B** followed by intermolecular trapping of **B** with 'CF_3COO-' anion would furnish the *α*-acyloxyimine intermediate **C**. Alternatively, the formation of *α*-acyloxyimine **C** can also be envisaged from **A** through intramolecular rearrangement. Next, *α*-acyloxyimine **C** to product **2** could be visualized *via* the acid promoted semipinacol rearrangement.[16] Thus, electrophilic activation of **C** with TFA and subsequent stabilization by electron-rich aryl group would generate the intermediate phenonium ion **D**. Finally, oxygen lone pair assisted 1,2-migration of electron rich aryl group in **D** would generate the oxonium ion **E**, which on hydrolysis would furnish the *α*-amino ketones **2**.



Scheme 5. Plausible mechanism for the oxidative rearrangement of enamine **1**.

To prove the proposed mechanism, we envisioned the synthesis of *α*-acyloxyimine intermediate **C**. Thus, we synthesized the *α*-hydroxy aldehydes **4a**/**4b** from 2-hydroxyacetophenone (see supporting information). Various attempts to convert the aldehydes **4a**/**4b** to corresponding imines with tosylamide were unsuccessful, which is possibly due to the instability of the imines under the reaction conditions. Interestingly, the reaction of **4a**/**4b** with tosylamide and trifluoroacetic anhydride in DCE at room temperature furnished the product **2v** and **2s** respectively in moderate to good yield (Scheme 6). These studies favoured the formation of *α*-acyloxyimine intermediate **C** from **1** and PIFA followed by subsequent acid promoted semipinacol rearrangement to the target *α*-amino ketones **2**.



Scheme 6. Synthesis of *α*-amino ketones from *α*-hydroxy aldehydes.

Conclusions

We have demonstrated a new oxidative rearrangement of *p,p*-diarylenamine with hypervalent iodine reagent. The reaction enabled the synthesis of various *α*-amino ketones in good to excellent yield. During the oxidative rearrangement, electron rich aryl groups migrate with remarkably high chemoselectivity. Mechanistic investigation revealed the initial hypervalent iodine mediated oxidation of *β,β*-diarylenamine to *α*-acyloxyimine intermediate and subsequent acid promoted semipinacol rearrangement.

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Notes and references

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Electronic Supplementary Information (ESI) available: General experimental, reaction optimization data, and spectral copies of all the new compounds. See DOI: 10.1039/c000000x/

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