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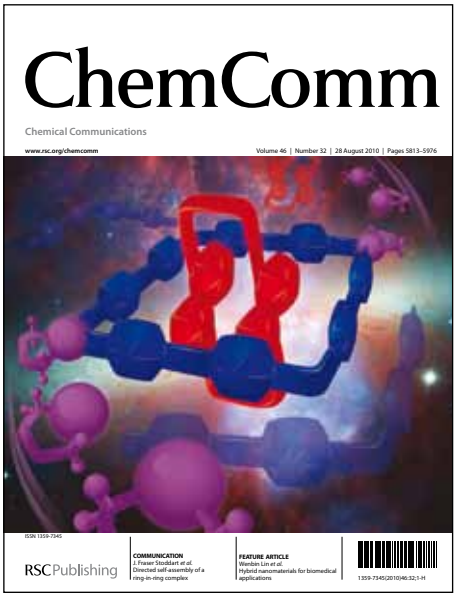

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ARTICLE TYPE

Efficient cyclization of tertiary amines and alkenes promoted by KO*t*-Bu/DMF

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

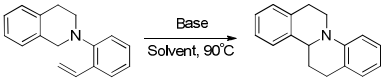
Nitrogen heterocycles could be prepared in good yields via intramolecular cyclization of tertiary amines and alkenes promoted by KO*t*-Bu/DMF.

Nitrogen heterocycles are most privileged structures in natural products and synthetic drugs. Their synthetic methods have been receiving great attention.[1] In recent years, there have been increasing interests in the direct functionalization of α C–H bonds of amines.[2] The strategy provides superior advantages over the traditional methods in terms of synthetic efficiency, atom economy and green chemistry. Typical activation modes of α C–H bonds of amines include α-amino anion pathway, α-amino cation (iminium) pathway, α-amino radical pathway, and transition metal mediated C–H activation pathway.[2] The generation of reactive α-amino radicals and consequent addition to alkenes are highly efficient for the synthesis of α-alkyl amines and nitrogen heterocycles.[3, 4] So far the generation of α-aminoalkyl radicals has been reported via the homolysis of α C–X bonds, radical translocation, photoinduced single electron transfer, and SmI_2-promoted reduction of imines or iminium cations.[5] However these methods still suffer from the limited substrate scope, toxic reagents, or the requirement of special precursors (such as α-sulfanyl amines or α-TMS amines) and light irradiation.

Knochel, Pines and their co-workers found that KO*t*-Bu could catalyze the addition of carbonyl derivatives (lactams, ketones, nitriles and imines) to styrene.[6] The carbanion reaction pathway was proposed by Pines et al.[6a] In 2008, Itami et al. reported the KO*t*-Bu promoted biaryl coupling of electron-deficient nitrogen heterocycles with aryl iodides.[7] Shi and other researchers found that the coupling reactions of aryl halides and arenes could be promoted by KO*t*-Bu in combination with 1, 10-phenanthroline or DMF.[8] Recently Hayashi, Rueping and their co-workers reported Mizoroki-Heck reaction promoted by KO*t*-Bu/DMF.[9] In these reactions, the generation of aryl radical via the single electron transfer from *t*-butoxy anion to aryl halides and the consequent elimination of halogen anion was suggested. In this paper, we report a new strategy for the generation of α-aminoalkyl radicals via the direct reaction of tertiary amines with KO*t*-Bu/DMF. The resulted α-aminoalkyl radicals readily undergo intramolecular cyclization with alkenes.

Initially we examined the reaction of *N*-2-ethenyl-phenyl tetrahydroisoquinoline **1a** in the presence of KO*t*-Bu (3 equiv) in DMF. The reaction gave 64% yield of cyclization product **2a** (Table 1, entry 1). DMSO is also suitable solvent and a slightly lower yield was obtained (Table 1, entry 2). The reaction in *N, N*-dimethylacetamide (DMA) led to poor yield (Table 1, entry 3). The combination of NaO*t*-Bu/DMF provided slightly lower yield (Table 1, entry 4). Sodium methoxide also provided poor yield (Table 1, entry 5). Potassium hexamethyldisilazide (KHMDS) could promote the reaction and **2a** was obtained in 56% yield (Table 1, entry 6), however the use of butyl lithium in THF did not give the product **2a** (Table 1, entry 7). Other solvents and bases were also examined, but no substantial amount of **2a** could be obtained.[10] The decrease of the loading of KO*t*-Bu (1.5 equiv) led to better yield (Table 1, entry 8). The use of substoichiometric amount of KO*t*-Bu (0.5 equiv) still gave good yield (Table 1, entry 9). The sublimed grade of KO*t*-Bu (>99.99% purity) was also examined and the similar yield was obtained (Table 1, entry 10). The fact supported that the reaction is promoted by KO*t*-Bu itself, rather than contaminated transition metals in KO*t*-Bu. The radical scavenger such as benzoquinone and TEMPO (2, 2, 6, 6-tetramethylpiperidinooxy)

Table 1 Intramolecular cyclization of **1a**[a]



1a **2a**

Entry	Solvent	Base	Yield (%)[b]
1	DMF	KO*t*-Bu	67 (64)
2	DMSO	KO*t*-Bu	62
3	DMA	KO*t*-Bu	11
4	DMF	NaO*t*-Bu	63
5	DMF	NaOMe	10
6	DMF	KHMDS	56
7[c]	THF	*n*-BuLi	0
8[d]	DMF	KO*t*-Bu	82 (76)
9[e]	DMF	KO*t*-Bu	78 (65)
10[f]	DMF	KO*t*-Bu	82 (69)
11[d,g]	DMF	KO*t*-Bu	0
12[d,h]	DMF	KO*t*-Bu	5
13[d,i]	DMF	KO*t*-Bu	31

[a] Reaction conditions: **1a** (0.1 mmol), base (0.3 mmol), solvent (1.2 mL), 90 °C, 4 h. [b] Yields were determined by GC with *n*-dodecane as the internal standard. The values in the parenthesis are the isolated yields after the column chromatograph. [c] **1a** (0.1 mmol), *n*-BuLi (0.3 mmol), THF (1.2 mL), -30 °C, 4 h. [d] KO*t*-Bu (0.15 mmol) was used. [e] **1a** (0.3 mmol), KO*t*-Bu (0.15 mmol). [f] KO*t*-Bu (>99.99% purity, 0.15 mmol) was used. [g] Benzoquinone (0.15 mmol) was used. [h] TEMPO (0.15 mmol) was added. [i] The reaction was carried out with an oxygen balloon.

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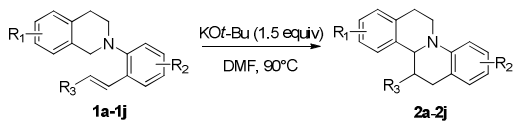
Table 2 Intramolecular cyclization of tetrahedroisoquinoline derivatives **1a**-**1j** promoted by KOt-Bu/DMF[a]



1a-1j **2a-2j**

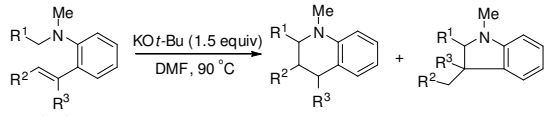
Entry	1	R^1	R^2	R^3	2	Yield (%)[b]
1	**1a**	H	H	H	**2a**	76
2	**1b**	H	3-Br	H	**2b**	68
3	**1c**	H	3-Cl	H	**2c**	75
4	**1d**	H	3-Me	H	**2d**	57
5[c]	**1e**	H	3-MeO	H	**2e**	52
6	**1f**	H	3-CF_3	H	**2f**	0
7	**1g**	H	4-NO_2	H	**2g**	0
8[c]	**1h**	6,7-$(MeO)_2$	H	H	**2h**	72
9	**1i**	H	H	Me	**2i**	85[d]
10	**1j**	H	H	di-Me	**2j**	84

[a] Reaction conditions: **1a**-**1j** (0.1 mmol), KO*t*-Bu (0.15 mmol), DMF (1.2 mL), 90 °C, 4 h. [b] Isolated yields after the column chromatograph. [c] KO*t*-Bu (0.3 mmol) and DMF (2 mL) were used. [d] The product was obtained as a mixture of *cis*- and *trans*-isomers (*cis*/*trans*=3:2).

significantly inhibited the reaction (Table 1, entries 11−12). The reaction was also inhibited in the presence of oxygen (Table 1, entry 13). The results undoubtedly implicated a free radical reaction pathway.

The reaction was also applied to other tetrahydroisoquinoline derivatives **1a**−**1j** and the results are summarized in Table 2. The reaction of **1b**−**1c** bearing with 3-halide styrene moiety gave the products **2b**−**2c** in good yields (Table 2, entries 2-3). The substitution with electron-donating groups such as methyl and methoxyl slightly decreased the yields (Table 2, entries 4-5). The reactions of substates **1f**−**1g** with trifluoromethyl and nitro groups did not provide the expected cyclization products (Table 2, entries 6-7), instead polmerized products were probably generated. The electron-deficient olefins may be prone to the polymerization under the reaction conditions. The substitution with methoxyl groups at the tetrahydroisoquinoline moiety was also tolerable. The product **2h** was obtained in good yield (Table 2, entry 8). The substitution of styrene moiety with β-methyl or β, β-dimethyl were also examined. The products **2i** and **2j** were obtained in good yields (Table 2, entries 9-10).

Table 3. Intramolecular cyclization of arylmethylamine derivatives **3a**-**3g** promoted by KO*t*-Bu/DMF. [a]



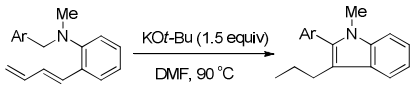
3a-3g **4a-4f** **5a-5f**

Entry	3	R^1	R^2	R^3	4/5	Yield (%)[b]
1	**3a**	Ph	H	H	29/71	84[c]
2	**3b**	Ph	Ph	H	0/100	82[d]
3	**3c**	Ph	H	Ph	100/0	80[e]
4	**3d**	2-Naphthyl	H	H	100/0	70
5	**3e**	2-Quinolyl	H	H	100/0	77
6	**3f**	2-Benzofuranyl	H	H	100/0	41
7	**3g**	H	H	H	--	nr[f]

[a] Reaction conditions: **3a**–**3g** (0.1 mmol) and KO*t*-Bu (0.15 mmol) in DMF (1.2 mL) at 90 °C for 4 h.. [b] Combined isolated yields of **4** and **5**. [c] **5a** (*cis*/*trans*=1:5). [d] Isomers (*cis*/*trans*=1:10). [e] Isomers (*cis*/*trans*=1:3.3). [f] No reaction.

The reaction was further extended to arylmethylamine derivatives **3a−3g** and the results are summarized in Table 3. The reaction of *N*-benzyl-*N*-methyl-2-vinylaniline **3a** gave a mixture of *6-endo* cyclization product **4a** and *5-exo* cyclization product **5a** (**4a/5a**=29/71) in good yield (Table 3, entry 1). The introduction of β-phenyl group significantly increased the selectivity for *5-exo* product (Table 3, entry 2). On the other hand, α-phenyl substituted substrate **3c** provided *6-endo* product exclusively (Table 3, entry 3). 2-Naphthylmethylamine, 2-quinolylamine and 2-benzofuranylamine derivatives **3d–3f** provided *6-endo* products (Table 3, entries 4−6). For these substrates, big steric hindrance strongly favors *6-endo-trig* cyclization pathway.[11] *N, N*-Dimethylamine derivatives **3g** was also examined and found to be unreactive (Table 3, entry 7). The activation of α C−H bond by the neighboring aryl group seems to be necessary for this transformation.

β-Vinyl substituted substrate **3h** and **3i** were also examined. Interestingly 3-propyl indole derivatives **6h** and **6i** were obtained in good yields (Scheme 1). In these cases, *5-exo-trig* cyclization occurred exclusively. The indole derivatives were generated after the rearrangement of the double bond.[12]

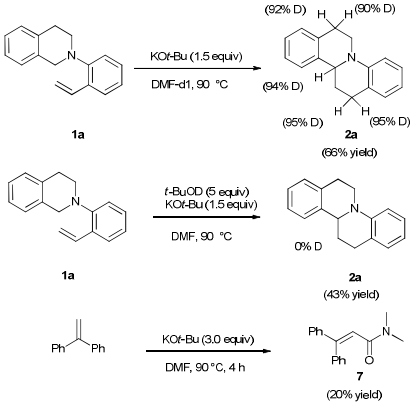


3h, Ar = Ph
3i, Ar = 2-Naphthyl

6h, 65% yield
6i, 80% yield

Scheme 1. Reaction of β-vinyl substituted substrates **3h** and **3i**.

When the reaction of **1a** was carried out in DMF-d_1, extensive deuterium incorporations at the benzyl positions were observed (Scheme 2). On the other hand, no deuteration was found if the reaction was carried out in non-deuterated DMF combined with 5 equivalents of *t*-BuOD. The results indicated that the reaction intermediate abstracts a hydrogen from DMF, but not from *t*-BuOH. If the reaction proceeds via an α-amino anion intermediate, the abstraction of a proton from more acidic *t*-BuOH should be favorable. The present evidence strongly supports a radical reaction pathway. Because *t*-butoxy radical is a possible intermediate in the reaction, we examined the general initiators of *t*-butoxy radical including *t*-BuOOBu-*t* and PhCOOOBu-*t* for the reaction of **1a**, however no **2a** was obtained.



Scheme 2. Study of reaction mechanism.

We reason that a radical derived from DMF plays the crucial role. Sliwka et al. observed the generation of radical intermediates in the basic DMF and DMSO solution via EPR

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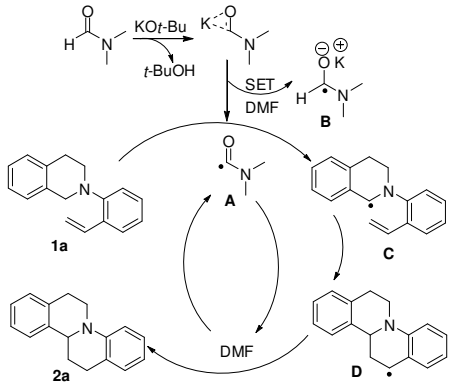
analysis, however the exact structures of these radical intermediates are not clear.[13] The trapping of the radical intermediate with 1,1-diphenylethylene was attempted (Scheme 2). To our delight, *N,N*-dimethyl-3,3-diphenylacrylamide **7** was obtained in 20% yield. The result together with the above deuterium-labeling experiment data suggest the generation of a carbamoyl radical from DMF. Such a carbamoyl radical was previously suggested in the oxidative reactions with *tert*-butyl hydroperoxide or *tert*-butyl perbenzoate in DMF.[14]

A tentative reaction mechanism is proposed in Scheme 3. The formation of the carbamoyl anions via the deprotonation of *N,N*-disubstituted formamides with lithium diisopropylamide or other strong bases had been reported by Reeves, Smith and their coworkers.[15] In the present reaction, DMF is probably deprotonated by KO*t*-Bu to give the carbamoyl anion with η^2 coordination of potassium by the carbonyl group. The anion is further transformed to the carbamoyl radical **A** by a single electron transfer process. The possible single electron acceptor may be another DMF molecule and a radical anion species such as **B** is formed. The radical **A** abstracts C-1 hydrogen atom of tetrahydroisoquinoline and the consequent radical cyclization provides the intermediate **D**. After the abstraction a hydrogen atom from DMF, the product **2a** is formed and the carbamoyl radical **A** is regenerated. Because the reaction proceeds via a chain process with the carbamoyl radical **A** being recycled, only a trivial amount of the radical anion **B** is formed depending on the chain length.



Scheme 3. Tentative reaction mechanism.

In summary, we have developed an efficient intramolecular cyclization of α-aryl substituted tertiary amines and alkenes promoted by KO*t*-Bu/DMF. The reaction provided a number of nitrogen heterocycles in good yields. The experiment results support a radical reaction pathway. The carbamoyl radical derived from DMF is proposed to be the crucial initiator in the reaction. Such a radical cyclization reaction promoted by the simple combination of KO*t*-Bu and DMF is unprecedented. The new pathway to reactive α-aminoalkyl radical should find wide applications for the direct functionalization of α C–H bonds of amines.

Notes and references

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†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/.

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10 See supporting information for the details of the screen of solvents and bases.

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