ORGANIC LETTERS

2013
Vol. 15, No. 23
6018–6021

Intramolecular Dehydrative Coupling of Tertiary Amines and Ketones Promoted by KO-*t*-Bu/DMF: A New Synthesis of Indole Derivatives

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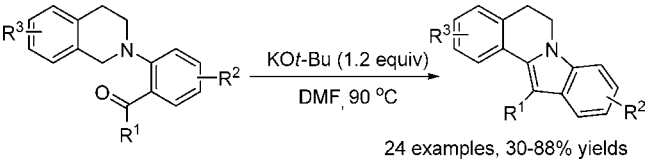
Received October 9, 2013

ABSTRACT



A new synthesis of indole derivatives has been achieved through intramolecular dehydrative coupling of tertiary amines and ketones promoted by KO-*t*-Bu/DMF. The reaction probably proceeds via an α-amino alkyl radical pathway.

Indole derivatives are abundant in natural products, synthetic drugs, and materials.[1] Their synthetic methods have attracted great attention during the past 100 years.[2,3] Although a number of successful methods have been developed, new synthetic approaches are still desirable considering the great structural diversity of indole derivatives. In recent years, there has been increasing interest in the direct functionalizations of α C−H bonds of amines.[4] The generation of reactive α-amino radicals and consequent reactions are highly efficient for the synthesis of α-alkyl amines and nitrogen heterocycles.[5] Rueping, Pandey, and Reiser et al. reported the generation of α-amino radicals via visible-light photoredox catalysis. The subsequent intramolecular conjugate addition to Michael acceptors gave indole derivatives in moderate yields.[6] Recently, we found that KO-*t*-Bu/DMF promotes the intramolecular cyclization of tertiary amines and alkenes.[7] The exploration of the reaction mechanism suggested the generation of α-amino alkyl radicals in this transformation. We speculate that nucleophilic α-amino alkyl radicals

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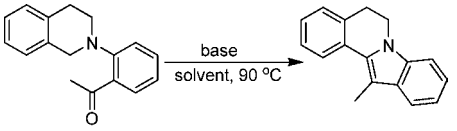
10.1021/ol402908m
Published on Web 11/20/2013

are also reactive with carbonyl groups. Herein, we report an intramolecular dehydrative coupling of tertiary amines and ketones promoted by KO-*t*-Bu/DMF. The reaction provides a new synthetic approach of 2-aryl indole derivatives.

Indolo[2,1-*a*]isoquinoline **2a** and its analogues possess a variety of interesting biological activities.[8] The reaction of 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde in the presence of a phosphazine base was reported to give indolo[2,1-*a*]isoquinoline in low yield.[8b] The generation of reactive α-aminoalkyl anion was proposed. Recently we developed a synthesis of **2a** via Ir-catalyzed dehydrative coupling of 1-(2-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)-ethanone **1a**; however, the yield is unsatisfactory.[9] Initially, we examined the reaction of **1a** in DMF with 3.0 equiv of KO-*t*-Bu at 90 °C. To our delight, **2a** was obtained in good yield. Furthermore, a number of bases and reaction solvents were examined and the results are summarized in Table 1. NaO-*t*-Bu, LiO-*t*-Bu, and NaOMe also promoted the reaction, but lower yields were obtained (Table 1, entries 2−4). KOMe provided a similar yield in comparison with KO-*t*-Bu (Table 1, entry 5). Other bases such as KOH, NaOH, K_2CO_3, and NaH were also tested, but no **2a** was obtained in substantial amounts. The reaction solvent was also investigated. *N,N*-Dimethylacetamide (DMA) and DMSO are also applicable, but lower yields were observed (Table 1, entries 6 and 7). Other solvents such as dioxin, toluene, $ClCH_2CH_2Cl$, CH_3CN, THF, *t*-BuOH, and glycol are incompatible with the reaction. No product **2a** could be obtained in these solvents.

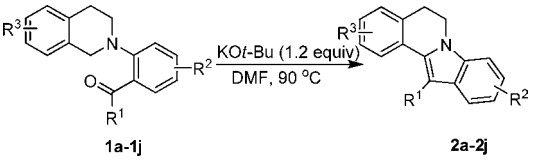
Table 1. Intramolecular Dehydrative Coupling of **1a**[a]

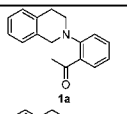
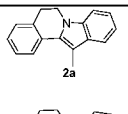
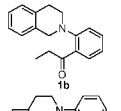
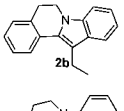
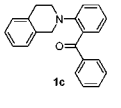
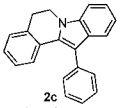
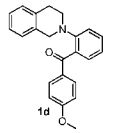
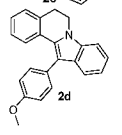
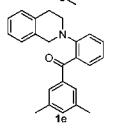
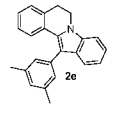
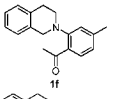
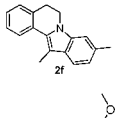
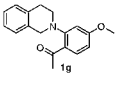
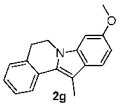
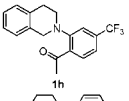
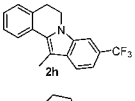
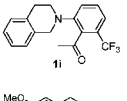
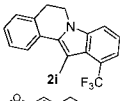
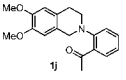
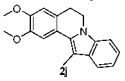


entry	base (equiv)	solvent	time (h)	yield[b] (%)
1	KO-*t*-Bu (3.0)	DMF	1	76
2	NaO-*t*-Bu (3.0)	DMF	1	57
3	LiO-*t*-Bu (3.0)	DMF	1	47
4	NaOMe (3.0)	DMF	1	63
5	KOMe (3.0)	DMF	1	76
6	KO-*t*-Bu (3.0)	DMA	1	71
7	KO-*t*-Bu (3.0)	DMSO	1	60
8	KO-*t*-Bu (1.5)	DMF	3	81
9	KO-*t*-Bu (1.2)	DMF	3	85
10	KO-*t*-Bu (1.0)	DMF	3	74
11	KO-*t*-Bu (0.5)	DMF	5	28
12[c]	KO-*t*-Bu (1.2)	DMF	3	81
13[d]	KO-*t*-Bu (1.2)	DMF	5	53
14[e]	KO-*t*-Bu (1.2)	DMF	10	-
15[f]	KO-*t*-Bu (1.2)	DMF	10	20

[a] Reaction conditions: **1a** (0.1 mmol), base, solvent (1 mL), at 90 °C under an argon atmosphere. [b] GC yields. [c] Reaction was carried out at 120 °C. [d] Reaction was carried out at 60 °C. [e] Reaction was carried out under an oxygen atmosphere. [f] TEMPO (0.12 mmol) was added.

Table 2. Intramolecular Coupling of Tetrahydroisoquinoline Derivatives **1a**−**j**[a]



entry	substrate	product	yield (%)[b]
1			83
2			88
3			75
4			60
5			65
6			69
7			88
8			83
9			82
10			71

[a] Reaction conditions: **1a**−**j** (0.2 mmol), KO-*t*-Bu (0.24 mmol), DMF (2.0 mL), at 90 °C under an argon atmosphere, 3 h. [b] Isolated yields.

The effect of KO-*t*-Bu loading was also examined. The best yield was obtained with 1.2 equiv of KO-*t*-Bu (Table 1, entries 8−11). The use of a substoichiometric amount of KO-*t*-Bu led to a significant loss of the yield (Table 1, entry 11). The reaction at 120 and 60 °C gave inferior yields

(8) For the synthesis and biological activity of indolo[2,1-α]isoquinolines, see: (a) Lötter, A. N. C.; Pathak, R.; Sello, T. S.; Fernandes, M. A.; Otterlo, W. A. L. V.; Koning, C. B. D. *Tetrahedron* **2007**, *63*, 2263. (b) Kraus, G. A.; Gupta, V.; Kohut, M.; Singh, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5539. (c) Mahoney, S. J.; Fillion, E. *Chem.—Eur. J.* **2012**, *18*, 68.

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(Table 1, entries 12 and 13). The aminoalkyl anion is the proposed intermediate when sterically hindered phosphazine (super base) is used.[8b] However in the present reaction, the basicity of KO-*t*-Bu is not enough to remove the C1-proton. The control test indicated that the reaction is inhibited by oxygen and radical scavenger TEMPO (Table 1, entries 14 and 15). The results implicate a radical reaction pathway.

With the optimal reaction conditions in hand, the reaction was extended to a variety of tetrahydroisoquinoline derivatives, and the results are summarized in Table 2. 2-Tetrahydroisoquinolinylpropiophenone **1b** provided **2b** in a good yield (Table 2, entry 2). The reaction of 2-tetrahydroisoquinolinyl diphenyl ketone **1c** gave **2c** in a moderate yield (Table 2, entry 3). Interestingly, a small amount of benzophenone was also isolated in this case. This compound is probably generated via the fragmentation of the α-amino alkyl radical intermediate. Phenyl aryl ketones **1d** and **1e** are also applicable. Products **2d** and **2e** were obtained in moderate yields (Table 2, entries 4 and 5). The substitutions at the *N*-phenyl of **1a** with electron-withdrawing groups or electron-donating groups are tolerated very well. Excellent yields were obtained for substrates **1f**–**i** (Table 2, entries 6–9). Tetrahydroisoquinoline derivative **1j** with 1,2-dimethoxy substitution also provided product **2j** in good yield (Table 2, entry 10).

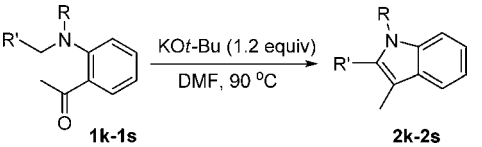
The reaction is not limited to tetrahydroisoquinoline derivatives. Benzylamine-derived ketones were also examined, and the results are summarized in Table 3. The *N*-substitutent was found to exert a strong effect on the reaction. No expected product was obtained for secondary amine (Table 3, entry 1).

When the *N*-substitutent is methyl, ethyl, phenyl, or benzyl, respectively, the indole products were obtained in good yields (Table 3, entries 2–5). 2-Naphthylmethylamine-, 4-bromobenzylamine-, and 3,4-dimethoxybenzylamine-derived ketones **1p**–**r** also gave products **2p**–**r** in good yields (Table 3, entries 6–8). Bis(4-methoxylbenzyl)amine-derived substrate **1s** provided the product **2s** in moderate yield (Table 3, entry 9).

Bis(4-trifluoromethyl-benzyl)amine-derived substrate **1t** gave the product **2t** in low yield, but 3-hydroxyindoline **2t′** was obtained in 50% yield (Scheme 1, eq 1). The compound **2t′** could be transformed to **2t** after treatment with 4-toluenesulfonic acid.[10] Interestingly, amide-derived ketones **1u** and **1v** provided 3-methyleneindolines **3u**–**v** in good yields (Scheme 1, eq 2). The *N*-acyl group obviously disfavors 1,2-dehydration of the alcohol intermediates; instead, 3-*exo*-dehydration occurs exclusively.

Tetrahydroisoquinoline-derived benzaldehydes **1w**–**x** were also examined (Scheme 2). The expected products **2w**–**x** were obtained in low yields. In addition, alcohols **4w** and **4x** were also isolated. In these cases, Cannizzaro reaction competed with the coupling reaction and led to the compounds **4w**–**x**.[11]

Table 3. Intramolecular Coupling of Arylmethylamine-Derived Substrates **1k**–**s**[a]



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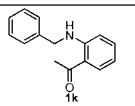
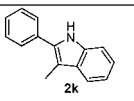
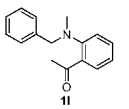
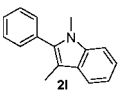
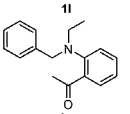
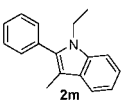
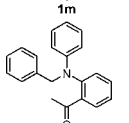
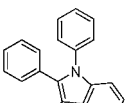
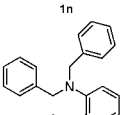
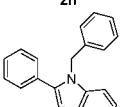
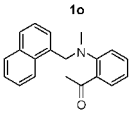
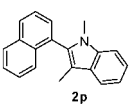
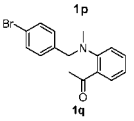
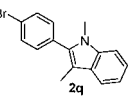
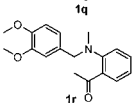
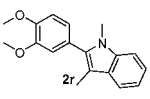
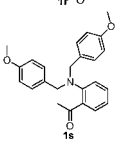
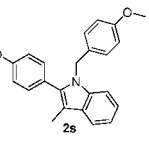
1			0
2			80
3			84
4			77
5			83
6			78
7			78
8			84
9			65

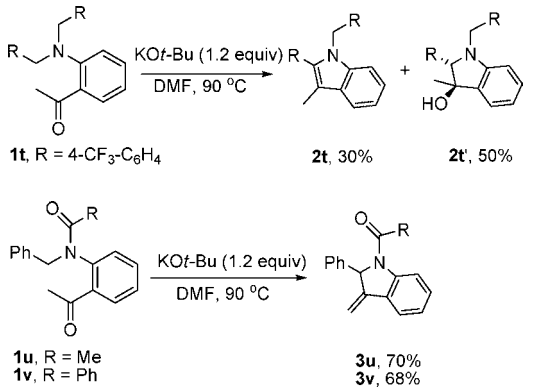
[a] Reaction conditions: **1k**–**s** (0.2 mmol), KO-*t*-Bu (0.24 mmol), DMF (2.0 mL), at 90 °C under an argon atmosphere, 3 h. [b] Isolated yields.

A tentative reaction mechanism is suggested in Scheme 3.[7,12] The carbamoyl radical **A** is generated by the deprotonation and subsequent single-electron transfer (SET) process. The radical **A** abstracts C-1 hydrogen of **1a** and the resulting α-amino alkyl radical **C** adds to the carbonyl group. The intermediate **D** abstracts a hydrogen from DMF. 3-Hydroxyindoline intermediate **E** is formed as

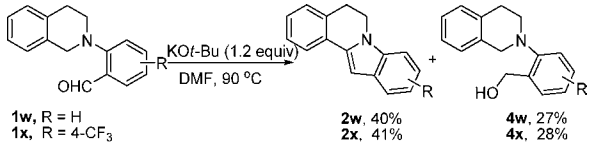
(10) **2t′** could be converted slowly to **2t** under the standard reaction conditions.

(11) The reaction mixtures of **1w**–**x** were carefully analyzed; however, the expected carboxylic acid products from the Cannizzaro reaction could not be found. We prepared 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzoic acid via the oxidation of **1w**. This acid was found to decompose under the reaction conditions.

Scheme 1. Intramolecular Coupling of Substrates **1t**–**v**



Scheme 2. Intramolecular Coupling of Substrates **1w**–**x**

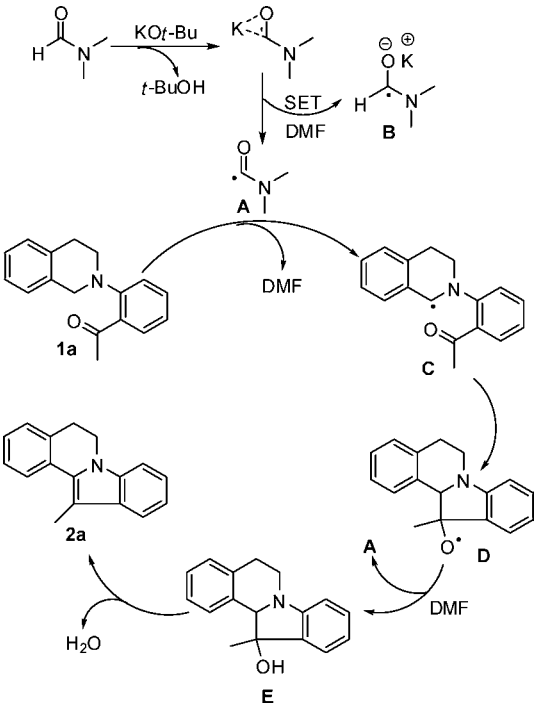


the primary product. In addition, the radical **A** is regenerated. The final product **2a** is generated after the dehydration of **E**.

In conclusion, we have developed a new intramolecular dehydrative coupling reaction of tertiary amines and ketones. The reaction is efficiently promoted by the combination of KO-*t*-Bu and DMF. A number of 2-arylindoles were prepared in good yields. A reaction mechanism via an α-aminoalkyl radical intermediate is suggested.

(12) The reactions with DMA and DMSO as the solvents (Table 1, entries 6 and 7) are suggested to proceed via similar free-radical pathways. The deprotonation of DMSO and DMA provides the corresponding α-carbonyl and α-sulfonyl carbon anions, which are further transformed to α-carbonyl and α-sulfonyl radicals via the subsequent single-electron transfer step. These radical intermediates initiate the dehydrative coupling reaction. Sliwka and co-workers observed the generation of radical intermediates in the basic DMF and DMSO solution via EPR analysis; see: Øpstad, C. L.; MelØ, T. B.; Sliwka, H. R.; Partali, V. *Tertrahedron* **2009**, *65*, 7616.

Scheme 3. Tentative Reaction Mechanism



The carbamoyl radical generated from DMF probably works as the crucial initiator. The reaction provides a practical synthesis of 2-arylindoles from *N*-arylmethyl-2-aminophenyl ketones.

Acknowledgment. We thank the National Natural Science Foundation of China (Nos. 20972195, 21172270) and Guangdong Engineering Research Center of Chiral Drugs for financial support of this study.

Supporting Information Available. Experimental procedures and full spectroscopic data of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.