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COMMUNICATION

One-pot synthesis of carbazoles from cyclohexanones and arylhydrazine hydrochlorides under metal-free conditions†

Fuhong Xiao, Yunfeng Liao, Mingyue Wu and Guo-Jun Deng*

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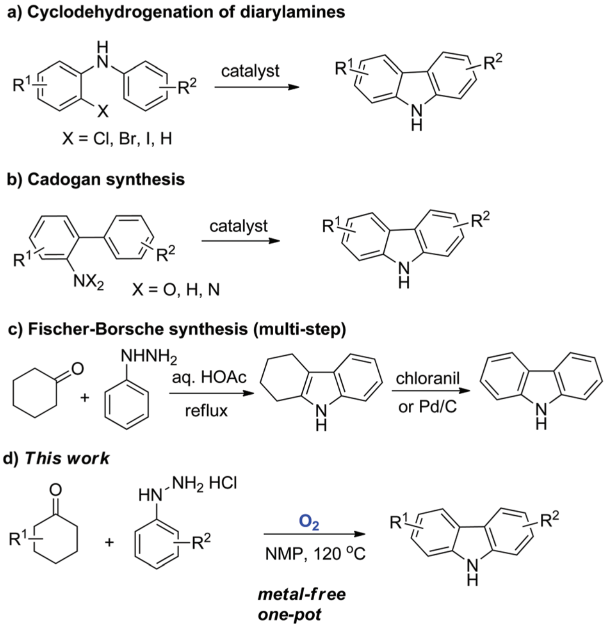
One-pot synthesis of carbazoles from cyclohexanones and arylhydrazine hydrochlorides is disclosed. Various substituted carbazoles were obtained in moderate to good yields *via* a sequence of condensation, cyclization and dehydrogenation under metal free conditions using molecular oxygen as an oxidant.

Carbazoles represent a key structural motif in a wide variety of natural products and pharmacologically active drugs,[1] as well as in materials chemistry like polymeric light-emitting diodes (PLED) and organic light-emitting devices (OLED).[2] Although there are a large number of classical and modern methods for the synthesis and structural modification of the carbazole scaffold, the development of alternative approaches for straightforward preparation of structurally diverse carbazoles is a field of constant interest.[3]

In recent years, the transition-metal-catalyzed carbazole synthesis has gained great interest. Among them, the palladium-catalyzed oxidative intramolecular cyclodehydrogenation of diarylamines is an efficient procedure to form carbazoles (Scheme 1a).[4,5] The diarylamines used for this approach are mainly prepared by the Ullmann–Goldberg coupling or the Buchwald–Hartwig protocol.[6] Recently, one-pot carbazole synthesis from anilines and 1,2-dihaloarenes *via* a domino N–H/C–H bond activation by palladium catalysts has been developed.[7] The deoxygenative cyclization of *o*-nitrobiphenyls in triethylphosphite which is known as the Cadogan synthesis is an alternative approach to carbazoles (Scheme 1b).[8] Recently, this transformation has been carried out more efficiently using carbon monoxide or triphenylphosphine and analogues as stoichiometric reducing agents.[9] Similar to *o*-nitrobiphenyls, *o*-aminobiphenyls and their analogues also can be used as starting materials for intramolecular aminations to afford various carbazoles under transition-metal-catalyzed reaction conditions.[10] In addition to the methods described above, several alternative procedures for the construction of the carbazole framework have also been developed.[11]



Scheme 1 Various approaches for carbazoles.

In fact, at the early stage, the carbazole synthesis mainly relies on the Fischer–Borsche synthesis using arylhydrazines and cyclohexanones *via* a multi-step procedure (Scheme 1c). This procedure involves condensation of arylhydrazines and cyclohexanones under acidic conditions and subsequent cyclization of arylhydrazones to form an indole moiety (tetrahydrocarbazole). The final dehydrogenation of tetrahydrocarbazole using palladium on activated carbon or chloranil (a strong oxidant) yields the desired product.[12,13] Cyclohexanones and arylhydrazines are readily available and stable compounds, thus the one-pot synthesis of substituted carbazoles from these compounds using environmentally benign oxidants such as molecular oxygen would be highly desirable.[14] Recently, the research groups of Stahl and Huang developed various Pd-catalyzed mild aerobic dehydrogenation reactions of cyclohexanones and ketones/aldehydes using oxygen as the sole oxidant.[15] We and others further extended this strategy for direct construction of diarylamines and aromatic ethers using cyclohexanones as aryl sources.[16] However, the dehydrogenation of cyclohexanone under metal-free conditions is rare. Herein, we report a one-pot synthesis of carbazoles from cyclohexanones and arylhydrazine

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Key Laboratory for Environmentally Friendly Chemistry and Application of Ministry of Education, College of Chemistry, Xiangtan University, Xiangtan 411105, China. E-mail: gjdeng@xtu.edu.cn; Fax: (+86) 731-58292477

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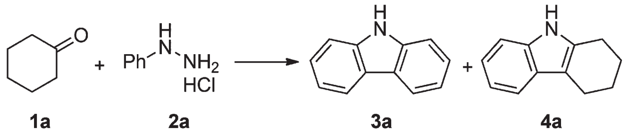
Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	Temp. (°C)	Yield[b] (%)	
			3a	**4a**
1	DMSO	140	12	0
2	Diglyme	140	12	Trace
3	Toluene	140	5	62
4	PhCl	140	28	32
5	Xylene	140	34	37
6	Anisole	140	53	8
7	DMF	140	70	0
8	DMA	140	72	0
9	NMP	140	76	0
10[c]	NMP	140	37	31
11[d]	NMP	140	7	62
12	NMP	100	34	37
13	NMP	50	0	70
14[e]	NMP	140	86	0
15[f]	NMP	140	0	0

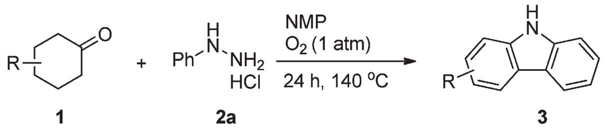
[a] Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), solvent (0.4 mL), 24 h under oxygen unless otherwise noted. [b] GC yield. [c] Under air. [d] Under argon. [e] 0.3 mmol of **2a** was used. [f] Phenylhydrazine instead of **2a** was used.

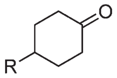
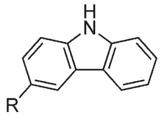
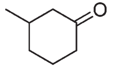
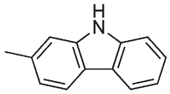
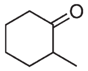
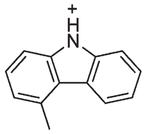
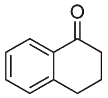
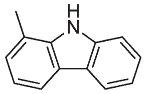
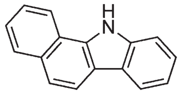
hydrochlorides using oxygen as an oxidant under metal-free conditions (Scheme 1d).

To initiate our study, the reaction of cyclohexanone (**1a**) with phenylhydrazine hydrochloride (**2a**) was chosen as a model in the absence of a metal-catalyst. Solvent played an important role in this transformation. The reaction of cyclohexanone (**1a**) and phenylhydrazine hydrochloride (**2a**) afforded the desired product carbazole (**3a**) in low yield in DMSO and diglyme as determined by GC and ^{1}H NMR methods (Table 1, entries 1 and 2). The reactions in toluene, chlorobenzene and xylene mainly afforded adduct tetrahydrocarbazole (**4a**). The use of anisole significantly improved the reaction yield as well as selectivity of the product (Table 1, entry 6). The reaction yield could be further improved by using DMF and DMA as solvents (Table 1, entries 7 and 8). The best yield was obtained in NMP, and the desired product was obtained in 76% yield without the formation of **4a** (Table 1, entry 9). The reaction was less efficient in air and argon atmosphere (Table 1, entries 10 and 11). Decreasing the reaction temperature decreased the reaction yield of the desired product (Table 1, entries 12 and 13). No product was observed when the reaction was carried out at 50 °C. The ratio of cyclohexanone (**1a**) to phenylhydrazine hydrochloride (**2a**) also affected the reaction yield profoundly, and the reaction yield could be improved to 86% when the ratio of **1a** : **2a** was changed to 2 : 3 (Table 1, entry 14). The presence of an equal amount of acid is necessary to get satisfactory yields, and no desired product was formed when **2a** was replaced by phenylhydrazine (Table 1, entry 15).

With the optimized reaction conditions established, a number of substituted cyclohexanone derivatives were employed to react with **2a** (Table 2). The reactions with cyclohexanones bearing electron-donating groups (entries 2–5) and electron-withdrawing substituents (entry 7) at the *para* position proceeded smoothly to give the desired products in good yields. The position of the substituents on the cyclohexanone ring profoundly affected the reaction yield. Two products **3h** and **3h′** were obtained in a combination yield of 62% when 3-methylcyclohexanone was used (Table 2, entry 8). The reaction yield decreased dramatically when 2-methylcyclohexanone was used as the substrate (Table 2, entry 9). When 3,4-dihydronaphthalen-1-one (**1j**) was subjected to the procedure, the product was isolated in 80% yield (entry 10). In general, the reactions showed good selectivity and only trace amounts of tetrahydrocarbazole byproducts were observed.

Table 2 Reaction of **2a** with various cyclohexanones[a]

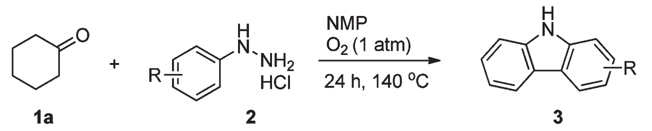


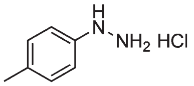
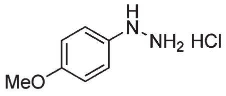
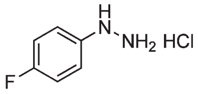
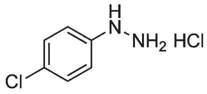
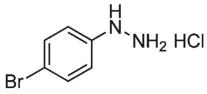
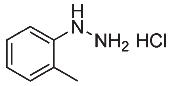
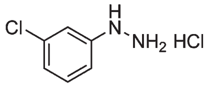
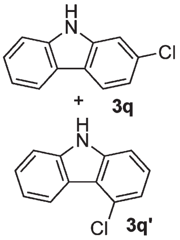
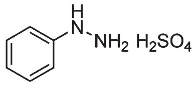
Entry	Cyclohexanone		Product		Yield[b] (%)
					
2	R = CH_3	**1b**		**3b**	75
3	R = Et	**1c**		**3c**	73
4	R = *n*-pentyl	**1d**		**3d**	74
5	R = *tert*-pentyl	**1e**		**3e**	77
6	R = Ph	**1f**		**3f**	68
7	R = CO_2Et	**1g**		**3g**	71
8		**1h**		**3h**	62 (**3h** : **3h′** = 5 : 1)
9		**1i**		**3h′**	Trace
10		**1j**		**3i**	80
				**3j**	

[a] Conditions: **1** (0.2 mmol), **2a** (0.3 mmol), solvent (0.4 mL), 140 °C, 24 h under oxygen. [b] Isolated yield based on **1**.

To further explore the scope of the reaction, a number of substituted phenylhydrazine derivatives were employed to react with cyclohexanone. Functional groups such as methyl and methoxy were well tolerated under the optimal reaction conditions (Table 3, entries 1 and 2). Furthermore, sensitive halogen substituents including fluoro, chloro and bromo were well tolerated, and the desired products were obtained in good yields (Table 3, entries 3–5). This allows further functionalization of the

Table 3 Reaction of **1a** with various arylhydrazines[a]

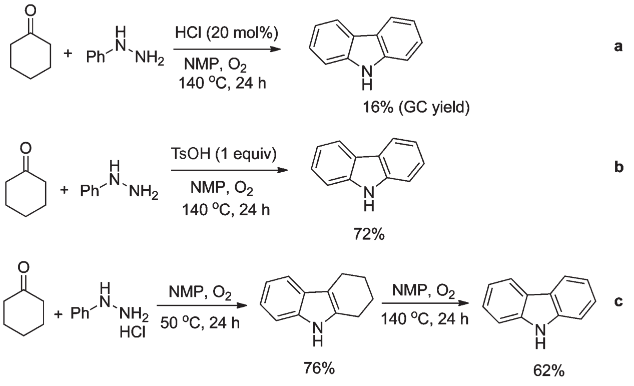


Entry	Aromatic hydrazine		Product	Yield[b] (%)
1		**2b**	**3k**	63
2		**2c**	**3l**	61
3		**2d**	**3m**	80
4		**2e**	**3n**	75
5		**2f**	**3o**	68
6		**2g**	**3p**	42
7		**2h**		58 (**3q** : **3q′** = 3 : 2)
8		**2i**	**3r**	72

[a] Conditions: **1a** (0.2 mmol), **2** (0.3 mmol), solvent (0.4 mL), 140 °C, 24 h under oxygen. [b] Isolated yield based on **1a**.

carbazole compounds. Again, the position of the substituents on the phenyl ring of phenylhydrazines significantly affected the reaction yields (Table 3, entries 6 and 7). To our delight, this reaction is not limited to arylhydrazine hydrochlorides. Phenylhydrazine sulfate was also reactive toward cyclohexanone and gave the desired products in 72% yield under similar reaction conditions (Table 3, entry 8).

To gather more information, some control experiments were set up under various reaction conditions (Scheme 2). As we mentioned previously, no carbazole (**3a**) was formed in the absence of acid and the addition of 20 mol% of HCl could improve the reaction yield to 16% (Scheme 2a). The addition of TsOH was also effective and gave the desired product in 72% yield (Scheme 2b). As we previously indicated, tetrahydrocarbazole (**4a**) was obtained as the major product when the reaction was carried out at 50 °C. However, the desired product **3a** could be obtained in 62% yield when **4a** was further treated under the standard reaction conditions at 140 °C (Scheme 2c). These experiments indicated that the reaction should take a similar pathway to the Fischer–Borsche synthesis. However, acid additives and higher temperature are necessary to get satisfactory yields under metal-free and strong oxidant-free conditions.



Scheme 2 Control experiments under various conditions.

In summary, we have developed a one-pot synthesis of carbazoles from arylhydrazine hydrochlorides and cyclohexanones. Unlike the widely used Fischer–Borsche reaction, this method could be achieved in one-pot in the absence of a metal-catalyst. Molecular oxygen was used as an efficient oxidant. Reaction temperature and solvent played important roles in the reaction. Functional groups such as methyl, ethyl, methoxy, and ester were well tolerated under the optimized conditions. Further investigations including the scope and the mechanism of this reaction are in progress in our laboratory.

Acknowledgements

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