Heterocycles

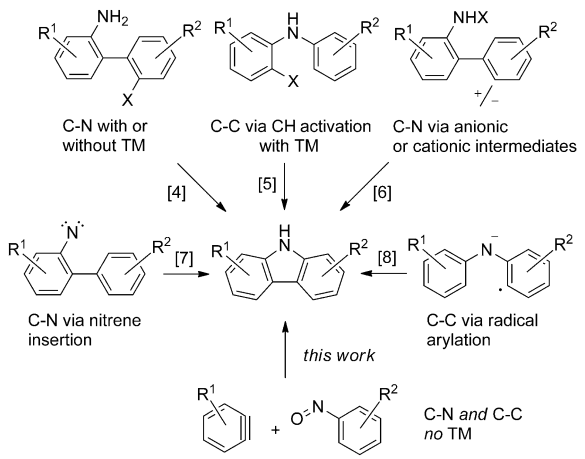
DOI: 10.1002/anie.201209447

Reactions of Arynes with Nitrosoarenes—An Approach to Substituted Carbazoles**

*Shyamal Chakrabarty, Indranil Chatterjee, Ludger Tebben, and Armido Studer**

The carbazole structural unit occurs in a large number of natural products that show interesting biological activity.[1] In addition, the carbazole moiety has also found application as a building block in materials science.[2] Although different valuable approaches to carbazoles have appeared,[1,3] owing to the importance of this substance class there is still demand for novel synthetic methods for its preparation. Some methods require the use of transition metals (TM). However, for biological studies, TMs have to be carefully removed from the final product. Also in the field of materials science, TM impurities might influence the physical properties of the targeted material. We therefore regard the development of transition-metal-free protocols for preparation of carbazoles as important.

In Scheme 1 different approaches for the construction of the carbazole core are depicted. C–N bond formation has been successfully used for the preparation of carbazoles[4] and



Scheme 1. Different approaches towards carbazoles.

C–C bond formation in diarylamines by means of TM-catalyzed C–H activation provides access to these important heterocycles.[5] Anionic or cationic cyclization through C–N bond formation also leads to the title compounds.[6] Intramolecular C–H insertion in biarylnitrenes is an alternative approach towards carbazoles[7] and also radical chemistry has been successfully used for their synthesis.[8] In all these methods the key step comprises the formation of a C–C or a C–N bond starting with an appropriately functionalized biaryl or diarylamine. In terms of synthetic flexibility, in particular for the synthesis of compound libraries, a two-component reaction where two bonds are sequentially formed would be more appealing. Indeed, this has already been achieved using TM-catalyzed cascades.[9] Herein we report unprecedented transition-metal-free two-component reactions of arynes with nitrosoarenes as a novel route to NH-carbazoles.[19]

Arynes have recently gained increased attention as reactive intermediates in multicomponent cascade reactions.[10,11] As part of our ongoing studies on the development of nitrosoarene chemistry,[12] we decided to study the reactivity of arynes towards nitrosoarenes. Arynes can be generated readily from the corresponding β-trimethylsilyltriflates.[13] We first investigated the reaction of benzyne derived from **1a** with nitrosobenzene (**2a**; Table 1).

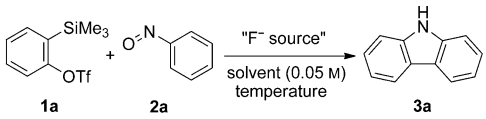
With KF/[18]crown-6 in THF and 2.1 equiv of **1a** at room temperature (RT) we obtained carbazole **3a** in 29% yield (Table 1, entry 1). The yield improved upon switching to dimethoxyethane (DME) as the solvent (Table 1, entry 2) but the reaction was less efficient at lower temperatures (Table 1, entries 3 and 4). Aryne generation with tetrabutylammonium fluoride (TBAF) delivered a lower yield (Table 1, entry 5) and a similar result was achieved when the reaction was conducted in DME with CsF as the fluoride source (Table 1, entry 6). The reaction was more efficient in acetonitrile (Table 1, entry 7) and a further improvement was noted in toluene in the presence of CsF/[18]crown-6 (Table 1, entry 8). The mixed solvent system toluene/CH_3CN turned out to be less suitable (Table 1, entry 11) and **3a** was not formed in dichloromethane or in toluene at higher temperature (Table 1, entries 9 and 10). The best yield (65%) was obtained upon diluting the reaction mixture, increasing the amount of **1a** in CH_3CN at room temperature, and using CsF (Table 1, entry 12). Further dilution led to a lower yield (Table 1, entry 13) and increasing the amount of **1a** did not alter reaction outcome to a large extent (Table 1, entry 14). In refluxing acetonitrile, product **3a** underwent further reaction with benzyne, and *N*-phenylcarbazole was isolated as side product in 16% yield along with **3a** (40% yield; Table 1, entry 15). The yield was lower when crown ether was added (Table 1, entry 16). Under optimized conditions (see Table 1, entry 12) the scope and limitations of the novel carbazole synthesis were studied.

Substituted nitrosoarenes were investigated keeping **1a** as the reaction partner. *ortho* Substitution was tolerated and the methyl derivative **3b** was isolated in 60% yield (Scheme 2). Increasing the size of the *ortho* substituent by switching to Et,

[*] S. Chakrabarty, Dr. I. Chatterjee, Dr. L. Tebben, Prof. Dr. A. Studer
NRW Graduate School of Chemistry
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität
Corrensstrasse 40, 48149, Münster (Germany)
E-mail: studer@uni-muenster.de

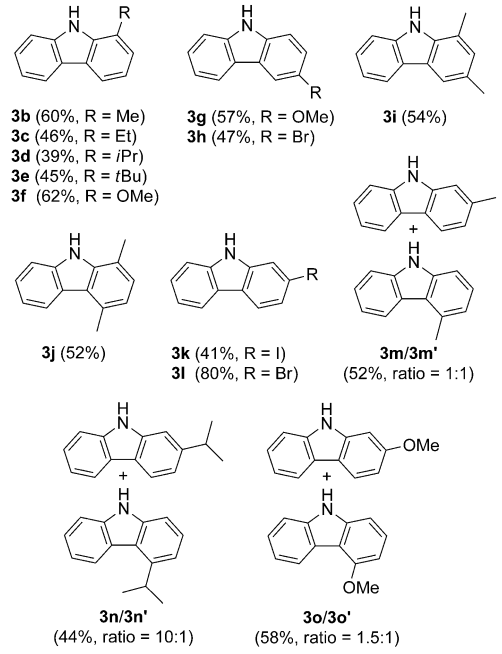
[**] We thank the DFG for supporting our work.

Table 1: Reaction of **1a** with **2a** under different conditions.



Entry	Equiv **1a**	Solvent	*T* [°C]	F^- source[a]	Yield [%][b]
1	2.1	THF	20	KF/[18]crown-6	29
2	2.1	DME	20	KF/[18]crown-6	40
3	2.1	DME	0	KF/[18]crown-6	25
4	2.1	DME	4	KF/[18]crown-6	37
5	1.8	THF	20	TBAF (1 M)	21
6	1.7	DME	20	CsF	23
7	1.7	CH_3CN	20	CsF	35
8	1.7	toluene	20	CsF/[18]crown-6	42
9	1.7	CH_2Cl_2	20	CsF	–
10	1.7	toluene	110	CsF	–
11	1.7	toluene/CH_3CN[c]	20	CsF	20
12	2.5	CH_3CN (0.025 M)	20	CsF	65
13	2.5	CH_3CN (0.015 M)	20	CsF	51
14	4.0	CH_3CN (0.025 M)	20	CsF	56
15	2.5	CH_3CN (0.025 M)	81	CsF	40[d]
16	4.0	CH_3CN (0.025 M)	20	CsF/[18]crown-6	49

[a] 2 equiv of fluoride source with respect to **1a** was used. [b] Traces of *N*-phenylcarbazole were identified by thin-layer chromatography in these reactions. [c] Ratio 3:1. [d] *N*-phenylcarbazole formed as side product in 16% yield.



Scheme 2. Variation of the nitroso component.

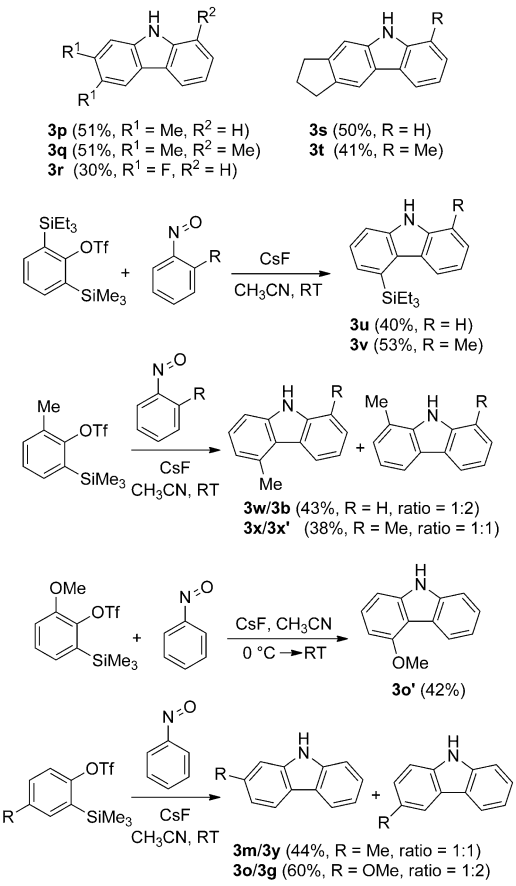
*i*Pr, and *t*Bu derivatives led to slightly lower yields (**3c**,[14] **3d**,[14] **3e**). The highest yield in this series was obtained with *o*-methoxy-substituted nitrosobenzene (**3f**; 62%). As expected, *para* substituents in the nitrososarenes were also tolerated (see **3g**, **3h**). Note that an aryl bromide functionality, which undergoes reaction in typical TM-mediated processes, was stable under the applied conditions. Surprisingly, nitrosoarenes bearing electron-withdrawing substituents such as the methoxycarbonyl or the nitro group at the *para* position did not react with the aryne (not shown). Reaction of 2,4-dimethylnitrosobenzene with benzyne afforded **3i** in 54% yield.[14]

We next addressed the regioselectivity of the novel two-component carbazole synthesis. Pleasingly, *m*-bromo-substituted nitrosobenzene reacted to give **3l** in high yield (80%) and with complete regioselectivity. Excellent regioselectivity but reduced yield was achieved with the I-substituted nitrosoarene (**3k**). The size of the substituent is important for obtaining high regioselectivity. Lower or no selectivity was achieved with *m*-isopropyl-, *m*-methoxy-, and *m*-methylnitrosobenzenes (**3m**/**3m′**, **3n**/**3n′**, and **3o**/**3o′**).

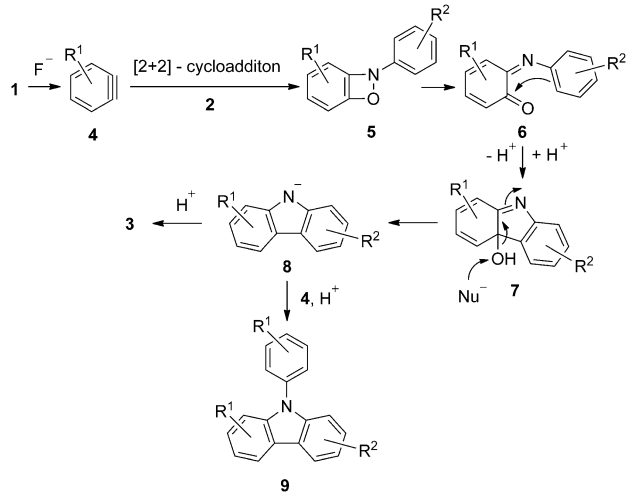
We also tested the substrate scope with respect to the aryne component and found that reaction of the symmetrical 4,5-dimethylbenzyne with nitrosobenzene and with *o*-methylnitrosobenzene delivered the corresponding carbazoles **3p** and **3q** each in 51% yield (Scheme 3). Similar results were achieved with the indane derivative (**3s**, **3t**). However, the electron-poorer 4,5-difluoroaryne reacted with nitrosobenzene in significantly lower yield (**3r**). A challenge in aryne chemistry is the control of the regioselectivity in the reaction with unsymmetrically substituted arynes. Pleasingly, 3-triethylsilylbenzyne[15] reacted with PhNO and *o*-TolNO with complete regiocontrol to provide the carbazoles **3u** and **3v**. However, the corresponding benzyne bearing the smaller methyl group reacted with poor selectivity (see **3w**/**3b** and **3x**/**3x′**). 3-Methoxybenzyne, which is known to be transformed with good to excellent regioselectivity in other processes,[16] reacted with PhNO to give **3o′** with complete regiocontrol. As expected, 4-substituted arynes did not show high regioselectivity in the reaction with nitrosobenzene (see **3m**/**3y** and **3o**/**3g**).

These studies indicated that the yield of the cascade reaction is influenced by the size of the *ortho* substituent and by electronic effects exerted by substituents at the nitroso component. Nitrosoarenes bearing π-electron-withdrawing substituents (methoxycarbonyl- and nitro-substituted derivatives) did not react. Since nitrosoarenes remained unchanged in such cases, likely the first step of the cascade (cycloaddition, see mechanism below) fails.

Our suggested mechanism for the cascade is depicted in Scheme 4. The intermediately generated aryne **4** first reacts with the nitroso component in a [2+2]-cycloaddition to provide the strained heterocycle **5**. Cycloreversion leads to the *o*-quinone derivative **6**. There is precedence for such cycloaddition/cycloreversion steps in aryne chemistry.[10c,d] Intermediate **6** can then undergo an intramolecular electrophilic aromatic substitution to give **7**. It is obvious that for systems bearing bulky *meta* substituents, cyclization occurs at



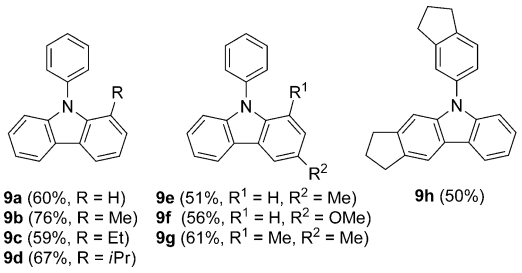
Scheme 3. Variation of the aryne component.



Scheme 4. Suggested mechanism.

the sterical less demanding distal 3-position with respect to the *meta* substituent. The C–O bond will be subsequently cleaved by a nucleophile[17] to give **8**, which upon protonation eventually affords carbazole **3**. The high regioselectivity observed in the reaction with 3-triethylsilylbenzyne is set in the initial [2+2]-cycloaddition. It is known that this aryne reacts in cycloadditions with high selectivity for steric reasons.[15] Therefore, the bulkier NPh substituent should be oriented away from the triethylsilyl group such that the smaller O substituent is placed next to the silyl group. This is in agreement with the regiochemistry observed in the formation of **3u** and **3v**. The same regioselectivity was observed for reactions of the 3-methoxy- and 3-triethylsilylbenzyne with nitrosobenzene. These results further indicate that the processes proceed by means of an initial cycloaddition step, since in ionic processes these two arynes should lead to different regioisomers.[15] Moreover, the low selectivity achieved in the reaction with 4-substituted aryne precursors (see **3m**/**3y**) gives strong support that arynes occur as intermediates.

We found that the reactivity of the proposed intermediate **8** is influenced by the countercation and the solvent. Whereas for the CsF-mediated processes in CH_3CN N-arylation by the aryne is a minor side reaction (see above), this route becomes the major pathway if Bu_4N/Ph_3SiF_2 (TBAT) is used as the fluoride source. Reaction of **1a** (2.2 equiv) with nitrosobenzene in DME in the presence of TBAT (2.6 equiv) provided *N*-phenylcarbazole **9a** in 60% yield (see Scheme 4 and Scheme 5).[18] In analogy, in situ generated benzyne was transformed to the mono- and disubstituted *N*-phenylcarbazoles **9b–g** in 51–76% yield and the *N*-arylcarbazole **9h** (50%) was obtained by reaction of the corresponding symmetrically substituted aryne with nitrosobenzene.



Scheme 5. N-arylated carbazoles using the TBAT protocol.

In conclusion, we have reported a novel method for the synthesis of carbazoles. Nitrosoarenes and in situ generated arynes react in the absence of any transition metal to provide the corresponding carbazoles. The substrate scope is broad and reactions occur under mild conditions (room temperature). Depending on the fluoride source and the solvent, either NH-carbazoles (for CsF in CH_3CN) or N-arylated carbazoles (for TBAT in DME) are obtained. In these cascades, a C–C bond along with one or two C–N bonds are formed. The two-component approach presented is well suited for the preparation of carbazole libraries.

Received: November 26, 2012
Published online: January 31, 2013

Keywords: arynes · cycloaddition · heterocycles · nitrosoarene · synthetic methods

[1] H.-J. Knölker, K. R. Reddy in *The Alkaloids: Chemistry and Biology, Vol. 65* (Ed.: G. A. Cordell), Elsevier, Evanston, IL, **2008**, p. 1.

[2] J. Li, A. C. Grimsdale, *Chem. Soc. Rev.* **2010**, *39*, 2399.

[3] A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193.

[4] With TM: a) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7603; b) S. H. Cho, J. Yoon, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996. Without TM, see Ref. [4b].

[5] See literature cited in Ref. [3]. Recent papers: a) H.-J. Knölker, *Top. Curr. Chem.* **2005**, *244*, 115; b) R. Forke,, M. P. Krahl, T. Krause, G. Schlechtingen, H.-J. Knölker, *Synlett* **2007**, 268; c) R. Forke, A. Jäger, H.-J. Knölker, *Org. Biomol. Chem.* **2008**, *6*, 2481; d) K. K. Gruner, H.-J. Knölker, *Org. Biomol. Chem.* **2008**, *6*, 3902; e) H.-J. Knölker, *Chem. Lett.* **2009**, *38*, 8; f) C. Wang, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194.

[6] a) C.-Y. Liu, P. Knochel, *Org. Lett.* **2005**, *7*, 2543; b) W. Yang, J. Zhou, B. Wang, H. Ren, *Chem. Eur. J.* **2011**, *17*, 13665; c) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem.* **2011**, *123*, 8764; *Angew. Chem. Int. Ed.* **2011**, *50*, 8605.

[7] a) J. I. G. Cadogan, M. Cameron-Wood, *Proc. Chem. Soc.* **1962**, 361; b) R. J. Sundberg, *J. Org. Chem.* **1965**, *30*, 3604; c) A. W. Freeman, M. Urvoy, M. E. Criswell, *J. Org. Chem.* **2005**, *70*, 5014; d) J. T. Kuethe, K. G. Childers, *Adv. Synth. Catal.* **2008**, *350*, 1577; e) B. J. Stokes, B. Jovanovic, H. Dong, K. J. Richert, R. D. Riell, T. G. Diver, *J. Org. Chem.* **2009**, *74*, 3225; f) C.-Y. Liu, P. Knochel, *J. Org. Chem.* **2007**, *72*, 7106.

[8] M. E. Budén, V. A. Vaillard, S. E. Martin, R. A. Rossi, *J. Org. Chem.* **2009**, *74*, 4490.

[9] a) L. Ackermann, A. Althammer, *Angew. Chem.* **2007**, *119*, 1652; *Angew. Chem. Int. Ed.* **2007**, *46*, 1627; b) D. J. St. Jean Jr. , S. F. Poon, J. L. Schwarzbach, *Org. Lett.* **2007**, *9*, 4893; c) L. Ackermann, A. Althammer, P. Mayer, *Synthesis* **2009**, 3493; d) J. K. Laha, P. Petrou, G. D. Cuny, *J. Org. Chem.* **2009**, *74*, 3152.

[10] a) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem.* **2003**, *115*, 518; *Angew. Chem. Int. Ed.* **2003**, *42*, 502; b) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701; c) D. Peña, D. Perez, E. Guitian, *Angew. Chem.* **2006**, *118*, 3659; *Angew. Chem. Int. Ed.* **2006**, *45*, 3579; d) S. S. Bhojgude, A. T. Biju, *Angew. Chem.* **2012**, *124*, 1550; *Angew. Chem. Int. Ed.* **2012**, *51*, 1520; e) A. Bhunia, S. R. Yetra, A. T. Biju, *Chem. Soc. Rev.* **2012**, *41*, 3140; f) C. M. Gampe, E. M. Carreira, *Angew. Chem.* **2012**, *124*, 3829 – 3842; *Angew. Chem. Int. Ed.* **2012**, *51*, 3766 – 3778; g) P. M. Tadross, B. M. Stoltz, *Chem. Rev.* **2012**, *112*, 3550.

[11] Selected recent examples: a) H. Yoshida, T. Morishita, J. Ohshita, *Org. Lett.* **2008**, *10*, 3845; b) H. Yoshida, T. Morishita, H. Fukushima, J. Ohshita, A. Kunai, *Org. Lett.* **2007**, *9*, 3367; c) D. Soorukram, T. Qu, A. G. M. Barrett, *Org. Lett.* **2008**, *10*, 3833; d) I. Larrosa, M. I. Da Silva, P. M. Gomez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, A. G. M. Barrett, *J. Am. Chem. Soc.* **2006**, *128*, 14042; e) F. Sha, X. Huang, *Angew. Chem.* **2009**, *121*, 3510; *Angew. Chem. Int. Ed.* **2009**, *48*, 3458; f) K. M. Allan, C. D. Gilmore, B. M. Stoltz, *Angew. Chem.* **2011**, *123*, 4580; *Angew. Chem. Int. Ed.* **2011**, *50*, 4488; g) E. Yoshioka, S. Kohtani, H. Miyabe, *Angew. Chem.* **2011**, *123*, 6768; *Angew. Chem. Int. Ed.* **2011**, *50*, 6638; h) H. Yoshida, Y. Ito, J. Ohshita, *Chem. Commun.* **2011**, *47*, 8512; i) H. Yoshida, Y. Asatsu, Y. Mimura, Y. Ito, J. Ohshita, K. Takaki, *Angew. Chem.* **2011**, *123*, 9850; *Angew. Chem. Int. Ed.* **2011**, *50*, 9676.

[12] a) C. K. Jana, A. Studer, *Angew. Chem.* **2007**, *119*, 6662; *Angew. Chem. Int. Ed.* **2007**, *46*, 6542; b) C. K. Jana, A. Studer, *Chem. Eur. J.* **2008**, *14*, 6326; c) C. K. Jana, S. Grimme, A. Studer, *Chem. Eur. J.* **2009**, *15*, 9078; d) I. Chatterjee, C. K. Jana, M. Steinmetz, S. Grimme, A. Studer, *Adv. Synth. Catal.* **2010**, *352*, 945; e) I. Chatterjee, R. Fröhlich, A. Studer, *Angew. Chem.* **2011**, *123*, 11453; *Angew. Chem. Int. Ed.* **2011**, *50*, 11257.

[13] Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211.

[14] *ortho*-Phenyloxyphenyltrifluoromethylsulfone (**10**) derived from **1a**, and which could not be separated by silica gel chromatography, was formed as a side product in small amounts, see the Supporting Information.

[15] S. M. Bronner, J. L. Mackey, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2012**, *134*, 13966.

[16] In other processes *o*-methoxybenzyne reacted with high regioselectivity, see: P. M. Tadross, C. D. Gilmore, P. Bugga, S. C. Virgil, B. M. Stoltz, *Org. Lett.* **2010**, *12*, 1224.

[17] Since we did not identify any nitro compounds derived from the nitrosoarene, we exclude the possibility that the nitroso derivative acts as a nucleophile for deoxygenation. We currently assume the fluoride anion to be the nucleophile for that particular step. Note that we have to use an excess of the F^- source in these reactions.

[18] Reaction of **1a** (2.2 equiv) with nitrosobenzene in CH_3CN in the presence of TBAT (2.6 equiv) provided *N*-phenylcarbazole **9a** in 33% yield along with NH-carbazole **3a** in 22% yield.

[19] G. W. Steinhoff, M. C. Henry, *J. Org. Chem.* **1964**, *29*, 2808.

