N-Heterocyclic Carbenes

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Functionalized 4-Aminoquinolines by Rearrangement of Pyrazole N-Heterocyclic Carbenes**

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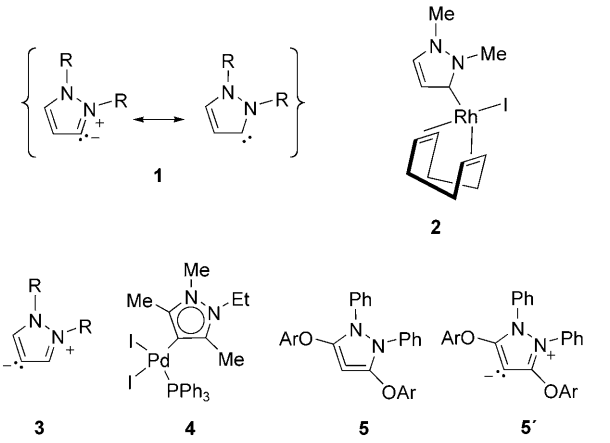
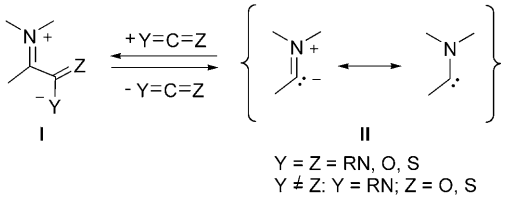
The quinoline[1] and pyrazole[2] class of substances feature diverse biological activities and other interesting properties. From the viewpoint of the chemistry of pharmacologically active compounds, considerable attention is being paid to 4-aminoquinolines, especially because after decades of use *Plasmodium falciparum* genotypes resistant to the active antimalarial compound chloroquine[3] have spread to almost all tropical regions of the world.[4] As the use of alternative active compounds is similarly restricted because of adverse effects or resistance,[5] variation of the substitution of 4-aminoquinolines still remains highly promising despite of the decoding of the genome of the pathogen in the meantime.[6] Herein we present a useful thermal rearrangement to new substituted 4-aminoquinolines starting from pyrazolium-3-carboxylates that proceeds by an N-heterocyclic carbene (NHC) of pyrazole. Carbenes of pyrazole and its relative, indazole,[7] have so far stood in the shadow of other NHCs.[8] In 1997, Herrmann's group described the rhodium complex **2** of pyrazol-3-ylidene **1**;[9] there have also been reports on the catalytic activities of iridium,[10] ruthenium,[11] and palladium complexes[12] of **1**.



The isomeric pyrazol-4-ylidene **3** can be construed as an rNHC ("remote N-heterocyclic carbene"[13]). The corresponding palladium complex **4** has been investigated regarding its activity in the Suzuki–Miyaura and Mizoroki–Heck reactions.[14] Whether the cyclic allene **5**[15] is more appropriately formulated as the mesomeric resonance structure **5′** and regarded as aromatic zwitterion[16] has recently been under discussion.[17]

Pseudo-cross-conjugated mesomeric betaines (PCCMB),[18] which contain the structural element **I**, readily cleave heterocumulenes on warming with formation of N-heterocyclic carbenes **II**. For example, NHCs of quinoline,[19] pyridine,[20] or imidazole[21] can be formed in situ by decarboxylation of the corresponding hetarenium-2-carboxylates; metal complexes may also be obtained in this way.[22] Conversely, trapping reactions of these carbenes with heterocumulenes to form 1:1-adducts has meanwhile become a classic reaction.[23]



Pyrazolium-3-carboxylates **7a–o** are also interesting precursors of pyrazol-3-ylidenes.[24] The alkylation of the 1-arylpyrazole-3-carboxylic esters **6a–o** to pyrazolium salts takes place in high yields with dimethylsulfate or diethylsulfate as an advantageous one-pot reaction in combination with subsequent hydrolysis to betaines **7a–o** (Scheme 1).[25] All of the betaines **7** are stable solids that lose water of crystallization at 100 °C (TGA and DSC measurements) and decarboxylate exothermally upon further heating (**7a**: at 115–120 °C) and then decompose. In toluene, however, even mild heating of **7a** at 34 °C leads to decarboxylation within a few hours and within 30 minutes under reflux with subsequent rearrangement to 4-aminoquinoline **8a**, which immediately precipitates in analytically pure form (Table 1, No. 1). Identical results were obtained in the aprotic solvents benzene and chlorobenzene, which also remove the stabilizing water of crystallization of the betaines as an azeotrope. The betaines are correspondingly stable in boiling 1-propanol or water.

As shown in Table 1, di- (**8a**,**b**), tri- (**8c–i**), tetra- (**8k**,**l**), and pentasubstituted quinolines (**8m–o**) can be obtained from the betaines **7a–o** by this rearrangement; of these compounds, only **8a** is known.[26] The substitution patterns realizable in

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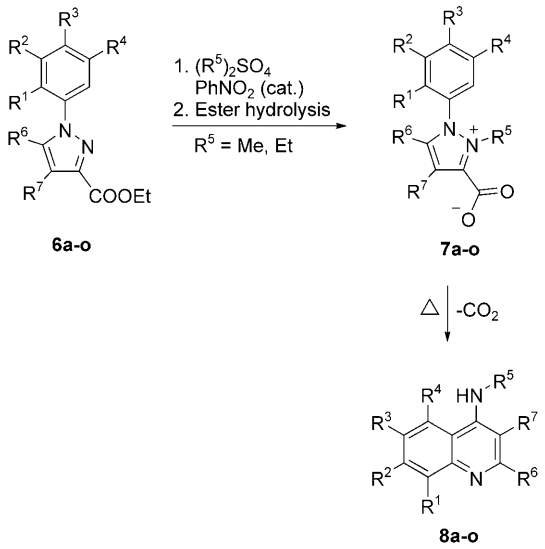
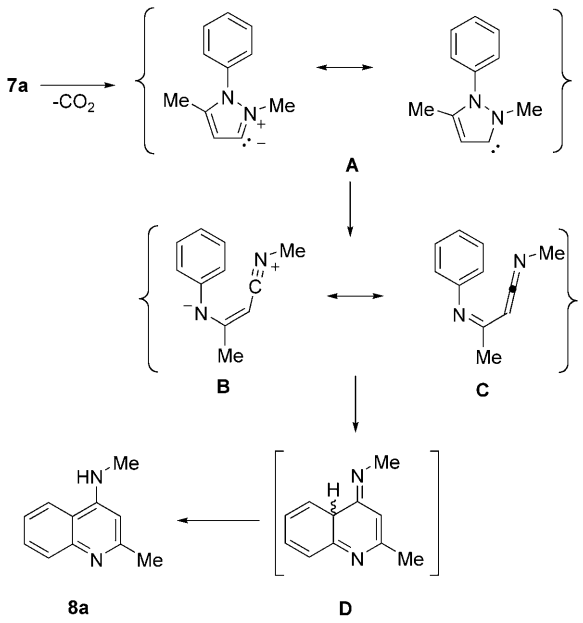


Scheme 1. Synthesis of the pyrazolium-3-carboxylates **7** as starting compounds for the rearrangement to quinolines **8**.



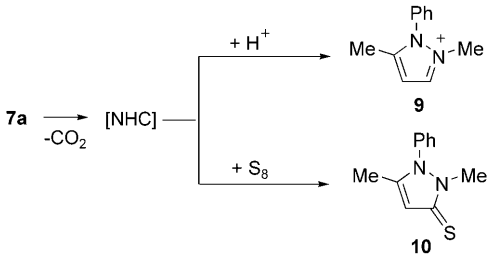
Scheme 2. Suggested mechanism for the rearrangement.

8f,**g**,**i**,**l** are very rare, and the C^2,N^4,C^5,Cl^6,O^8- (**8m**) and C^2,N^4,O^5,O^6,O^7 substitution patterns (**8n**,**o**) have not been reported before. Substitution of only one *m*-position of the phenyl ring of pyrazolium-3-carboxylate leads to a mixture of products, as expected: **8h** is thus obtained as an isomeric mixture in a 3:1 ratio. In agreement with the observed solvent effects, the acid function in the betaine **7j** prevents decarboxylation.

The reaction clearly proceeds by ring opening of the pyrazole-3-ylidene **A** formed by decarboxylation to the zwitterionic intermediate **B**, the non-polar mesomeric resonance structure of which is the keteneimine **C** (Schema 2). The subsequent ring closure to **D** can be seen as electrophilic aromatic substitution (of **B**) or 6π electrocyclization (of **C**). Tautomerization of **D** leads to the 4-aminoquinoline.

Along with signals for the pyrazolium ions **9**, $[\mathbf{A}+\mathrm{Na}]^+$ peaks for N-heterocyclic carbenes, such as **A**, were also detected by ESI mass spectrometry. Decarboxylation of **7a** in the presence of sulfur produced the thione **10** in 72% yield in a carbene trapping reaction (Scheme 3).

Attempts to trap the carbene formed from **7a** with 3,5-dichlorophenylisocyanate gave no pyrazolium-3-amidate, but



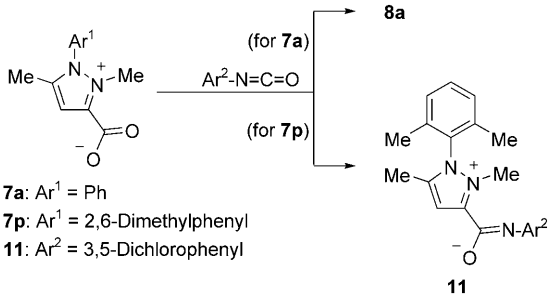
Scheme 3. Trapping reactions of the carbene to give **9** and **10**.

Table 1: Substitution pattern and yields in the sequence **6**→**7**→**8** (Scheme 1).

No.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	**7**	Yield [%]	**8**	Yield [%]
1	H	H	H	H	Me	Me	H	**7a**	89	**8a**	79
2	H	H	H	H	Me	2-thienyl	H	**7b**	66	**8b**	89
3	H	H	H	H	Et	Ph	Et	**7c**	55	**8c**	99
4	H	H	H	H	Me	Ph	Et	**7d**	81	**8d**	95
5	H	H	Me	H	Me	Me	H	**7e**	42	**8e**	65
6	H	H	Cl	H	Me	Me	H	**7f**	93	**8f**	59
7	H	H	Br	H	Me	Me	H	**7g**	54	**8g**	94
8	H	OMe	H	H	Me	Me	H	**7h**	94	**8h**[a]	54
9	F	H	H	H	Me	Me	H	**7i**	94	**8i**	30
10	COOH	H	H	H	Me	Me	H	**7j**	92	**8j**	0
11	Me	H	Cl	H	Me	Me	H	**7k**	96	**8k**	81
12	H	Cl	H	Cl	Me	Me	H	**7l**	49	**8l**	54
13	OMe	H	Cl	Me	Me	Me	H	**7m**	51	**8m**	37
14	H	OMe	OMe	OMe	Me	Me	H	**7n**	97	**8n**	87
15	H	OMe	OMe	OMe	Me	2-thienyl	H	**7o**	39	**8o**	58

[a] As mixture with its isomers.

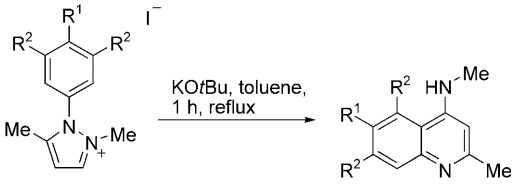
quinoline **8a** instead (Scheme 4). As the amidate contained the structure element **I** mentioned above, thermal cleavage of heterocumulenes occurs with regeneration of the carbene,



Scheme 4. The trapping reaction of the carbene to give amidate **11** if both *ortho* positions on Ar^1 are substituted.

which then rearranges immediately to the quinoline. The amidate is only then the main product when both *o*-positions of the aryl moiety on the pyrazolium-3-carboxylate are occupied: **11** was therefore obtained as stable adduct in high yield from the corresponding pyrazolium-3-carboxylate **7p** and 3,5-dichlorophenylisocyanate.

Control experiments showed that the pyrazolium salts **12**–**15** also rearrange to 4-aminoquinolines after treatment with base, although in lower yields (Scheme 5). The results of Schemes 3–5 allow us to favor the mechanism shown in Scheme 2 over an equally feasible Grob fragmentation of the betaines **7** to **8** without an intermediate carbene.



Scheme 5. Rearrangement starting from pyrazolium salts.

In summary, we present a new rearrangement of pyrazol-3-ylidenes produced in situ by decarboxylation of pseudo cross-conjugated mesomeric betaines to 4-aminoquinolines; the mechanism should generate interest from the viewpoint of heterocyclic and pharmaceutical chemistry.

Experimental Section

8a: Betaine **7a** (108 mg, 0.5 mmol) was suspended in toluene (4 mL) and heated to reflux for 30 minutes. The precipitate that formed was separated by filtration and washed with toluene. Yield: 79%, m.p. 234°C. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): $\delta = 8.07$ (d, 1H, 5-H, $J = 8.3$ Hz), 7.69 (d, 1H, 8-H, $J = 8.3$ Hz), 7.54 (dd, 1H, 7-H, $J = 6.9$ Hz, $J = 8.3$ Hz), 7.33 (dd, 1H, 6-H, $J = 8.3$ Hz, 6.9 Hz), 7.16 (q, 1H, *H*N, $J = 4.8$ Hz), 6.27 (s, 1H, 3-H), 2.87 (d, 3H, H_3CN, $J = 4.8$ Hz), 2.47 ppm (s, 3H, 2-CH_3); ^{13}C NMR ([D$_6$]DMSO, 100 MHz): $\delta =$ 159.2, 151.3, 148.3, 129.0, 128.8, 123.5, 121.7, 118.0, 98.2, 29.7, 25.7 ppm; ESI-MS: 173.1 (M+H$^+$, 100%); IR (KBr): $\tilde{\nu} = 3225$, 1594, 1561, 1443 cm^{-1}. HR-ESI-MS: calcd for $C_{11}H_{13}N_2$: 173.1079; found: 173.1076.

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[1] R. D. Larsen, D. Cai, *Science of Synthesis*, *Vol. 15*, Thieme, Stuttgart, **2004**, p. 389–496.
[2] B. Stanovnik, J. Svete, *Science of Synthesis*, *Vol. 12*, Thieme, Stuttgart, **2002**, p. 15–205.
[3] G. M. Findlay, *Recent Advances in Chemotherapy*, 3rd ed., Churchill, London, **1951**.
[4] a) D. C. Warhurst, *Curr. Sci.* **2007**, *92*, 1556–1560; b) E. A. Winzeler, *Nature* **2008**, *455*, 751–756; c) W. Peters, *Chemotherapy and Drug Resistance in Malaria*, Academic Press, London, **1987**; d) D. Payne, *Parasitol. Today* **1987**, *3*, 241–246; e) B. Greenwood, T. Mutabingwa, *Nature* **2002**, *415*, 670–672.
[5] a) K. Sanderson, *Nature* **2009**, DOI: 10.1038/news.2009.750; b) O. V. Miroshnikova, T. H. Hudson, L. Gerena, D. E. Kyle, A. J. Lin, *J. Med. Chem.* **2007**, *50*, 889–896.
[6] E. Paunescu, S. Susplugas, E. Boll, R. Varga, E. Mouray, I. Grosu, P. Grellier, P. Melnyk, *ChemMedChem* **2009**, *4*, 549–561.
[7] a) S. Scherbakow, J. C. Namyslo, M. Gjikaj, A. Schmidt, *Synlett* **2009**, 1964–1968; b) A. Schmidt, B. Snovydovych, *Synthesis* **2008**, 2798–2804; c) A. Schmidt, B. Snovydovych, S. Hemmen, *Eur. J. Org. Chem.* **2008**, 4313–4320; d) A. Schmidt, B. Snovydovych, T. Habeck, P. Dröttboom, M. Gjikaj, A. Adam, *Eur. J. Org. Chem.* **2007**, 4909–4916; e) A. Schmidt, T. Habeck, B. Snovydovych, W. Eisfeld, *Org. Lett.* **2007**, *9*, 3515–3518.
[8] a) F. E. Hahn, M. C. Jahnke, *Angew. Chem.* **2008**, *120*, 3166–3216; *Angew. Chem. Int. Ed.* **2008**, *47*, 3122–3172; b) *N-Heterocyclic Carbenes in Synthesis* (Ed: S. P. Nolan), Wiley-VCH, Weinheim, **2006**; c) F. A. Glorius, *Top. Organomet. Chem.* **2007**, *21*, 1–29; d) C. M. Crudden, D. P. Allen, *Coord. Chem. Rev.* **2004**, *248*, 2247–2273; e) W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342–1363; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309; f) T. Weskamp, V. P. W. Böhm, W. A. Herrmann, *J. Organomet. Chem.* **2000**, *600*, 12–22; g) D. Bourissou, O. Guerret, F. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39–92.
[9] a) C. Köcher, W. A. Herrmann, *J. Organomet. Chem.* **1997**, *532*, 261–265; b) W. A. Herrmann, J. Schütz, G. D. Frey, E. Herdtweck, *Organometallics* **2006**, *25*, 2437–2448.
[10] A. Prades, R. Corberán, M. Poyatos, E. Peris, *Chem. Eur. J.* **2008**, *14*, 11474–11479.
[11] A. Prades, M. Viciano, M. Sanaú, E. Peris, *Organometallics* **2008**, *27*, 4254–4259.
[12] J. Schütz, E. Herdtweck, W. A. Herrmann, *Organometallics* **2004**, *23*, 6084–6086.
[13] S. K. Schneider, P. Roembke, G. R. Julius, C. Loschen, H. G. Raubenheimer, G. Frenking, W. A. Herrmann, *Eur. J. Inorg. Chem.* **2005**, 2973–2977.
[14] a) Y. Han, L. J. Lee, H. V. Huynh, *Organometallics* **2009**, *28*, 2778–2786; b) Y. Han, H. V. Huynh, G. K. Tan, *Organometallics* **2007**, *26*, 6581–6585.
[15] V. Lavallo, C. A. Dyker, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2008**, *120*, 5491–5494; *Angew. Chem. Int. Ed.* **2008**, *47*, 5411–5414.

[16] M. Christl, B. Engels, *Angew. Chem.* **2009**, *121*, 1566 – 1567; *Angew. Chem. Int. Ed.* **2009**, *48*, 1538 – 1539.
[17] a) V. Lavallo, C. A. Dyker, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2009**, *121*, 1568 – 1570; *Angew. Chem. Int. Ed.* **2009**, *48*, 1540 – 1542; b) I. Fernández, C. A. Dyker, A. DeHope, B. Donnadieu, G. Frenking, G. Bertrand, *J. Am. Chem. Soc.* **2009**, *131*, 11 875 – 11 881.
[18] a) W. D. Ollis, C. A. Ramsden and S. P. Stanforth, *Tetrahedron* **1985**, *41*, 2239 – 2329; b) A. Schmidt, *Curr. Org. Chem.* **2004**, *8*, 653 – 670; c) A. Schmidt, *Adv. Heterocycl. Chem.* **2003**, *85*, 67 – 171; d) A. Schmidt, T. Habeck, A. S. Lindner, B. Snovydovych, J. C. Namyslo, A. Adam, M. Gjikaj, *J. Org. Chem.* **2007**, *72*, 2236 – 2239.
[19] a) H. Quast, E. Schmitt, *Justus Liebigs Ann. Chem.* **1970**, *732*, 43 – 63; b) H. Quast, E. Schmitt, *Justus Liebigs Ann. Chem.* **1970**, *732*, 64 – 69.
[20] a) A. R. Katritzky, R. Awartani, R. C. Patel, *J. Org. Chem.* **1982**, *47*, 498; b) A. R. Katritzky, H. M. Faid-Allah, *Synthesis* **1983**, 149 – 150.
[21] a) A. Schmidt, A. Beutler, M. Albrecht, B. Snovydovych, F. J. Ramírez, *Org. Biomol. Chem.* **2008**, *6*, 287 – 295; b) I. Tommasi, F. Sorrentino, *Tetrahedron Lett.* **2005**, *46*, 2141 – 2145.
[22] a) A. M. Voutchkova, L. N. Appelhans, A. R. Chianese, R. H. Crabtree, *J. Am. Chem. Soc.* **2005**, *127*, 17624 – 17625; b) A. Tudose, L. Delaude, B. André, A. Demonceau, *Tetrahedron Lett.* **2006**, *47*, 8529 – 8533.
[23] a) L. Delaude, *Eur. J. Inorg. Chem.* **2009**, 1681 – 1699; b) N. Kuhn, M. Steinmann, G. Weyers, *Z. Naturforsch. B* **1998**, *54*, 427 – 433; c) N. Kuhn, E. Niquet, M. Steimann, I. Walker, *Z. Naturforsch. B* **1999**, *54*, 1181 – 1187.
[24] A. Schmidt, T. Habeck, *Lett. Org. Chem.* **2005**, *2*, 297 – 307.
[25] A. Schmidt, T. Habeck, M. K. Kindermann, M. Nieger, *J. Org. Chem.* **2003**, *68*, 5977 – 5982.
[26] T. J. Egan, R. Hunter, C. H. Kaschula, H. M. Marques, A. Misplon, J. Walden, *J. Med. Chem.* **2000**, *43*, 283 – 291 and references therein.

