

# Nucleophilic Carbenes of Pyrazoles Starting from Pseudo-Cross-Conjugated Mesomeric Betaines

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**Abstract:** Pyrazolium-3-carboxylates, which belong to the class of pseudo-cross-conjugated heterocyclic mesomeric betaines, decarboxylate to give nucleophilic carbenes, which can be trapped as pyrazolium salts. An aldol addition, a Knoevenagel reaction, and a Cannizzaro-type reaction are presented, which are initiated by the strong basicity of the *in situ* generated pyrazol-3-ylidene.

**Keywords:** Decarboxylation, 1,2-ylide, pyrazol-3-ylidenes, pyrazolium-3-carboxylates.

Since the first isolation of a persistent nucleophilic carbene by Arduengo in 1991 [1], this class of compounds has attracted considerable attention. A variety of derivatives has been synthesised since then [2] and this has resulted in a remarkable development of imidazol-2-ylidenes as versatile ligands in transition metal complexes for use in catalysed reactions [3]. The synthesis of known nucleophilic carbenes starts either from the corresponding salts, which can be deprotonated with a strong base [1, 4], or from imidazolethiones with potassium in boiling THF [5]. 1,2,4-Triazol-5-ylidenes were obtained by thermal elimination of 5-methoxytriazoles *in vacuo* [6]. By these routes, imidazolidin-2-ylidenes, tetrahydropyrimidin-2-ylidenes, imidazol-2-ylidenes, 1,2,4-triazol-5-ylidenes, 1,3-thiazol-2-ylidenes, as well as acyclic carbenes have been generated [2]. Very few reports have appeared dealing with the decarboxylation of pseudo-cross-conjugated heterocyclic mesomeric betaines (PCCMB) [7], which is one of the four distinct categories of this class of compounds [8]. Only this type of conjugation in mesomeric betaines seems to enable the decarboxylation under relatively mild conditions and the formation of nucleophilic carbenes [8], which have been postulated as reactive intermediates in the Hammick reaction [9]. Some very interesting reports of the reverse process deal with trapping experiments of imidazol-2-ylidenes with carbon dioxide [10].

In continuation of our interest in mesomeric betaines [11] and ionic species [12] we report here the generation and chemistry of pyrazol-3-ylidenes. Recently, we described the synthesis and some properties of the pseudo-cross-conjugated mesomeric betaine pyrazolium-3-carboxylate (**2**) [13] as a model compound of the alkaloid Nigellicin (**1**) from *Nigella sativa* [14]. This betaine, which crystallises with one water of crystallisation as evidenced by elemental analysis and X-ray crystallography, can be methylated to give an ester (**3**) with methyl iodide, and protonated with HBF<sub>4</sub> to give the pyrazolium-3-carboxylic acid (**4**) (Fig. (1)).

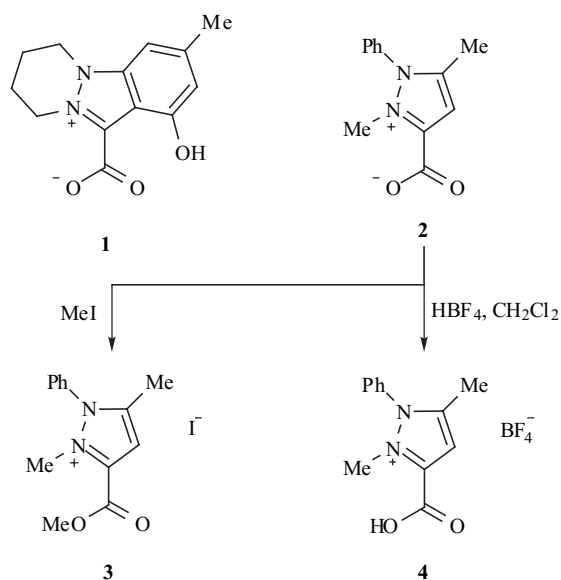


Fig. (1).

Decarboxylation of the betaine (**2**) results in the formation of the nucleophilic carbene (**5**), which gives the pyrazolium salt (**6**) on trapping with protons (Fig. (2)). Correspondingly, in the ESI mass spectra measured by spraying a sample of **2** from methanol, the pyrazolium salt (**6**) is detectable at  $m/z = 173$  u as the base peak. An additional peak at  $m/z = 345$  u can be assigned to the dimerised carbene [**5** + **5** + H]<sup>+</sup>. Spraying a 1:1 mixture of the betaine (**2**) and silver trifluoromethanesulfonate from methanol gives a prominent peak at  $m/z = 451$  u, which corresponds to the masses of the pyrazol-3-ylidene silver complex [**5** + **5** + Ag]<sup>+</sup> similar to the complexes described for other nucleophilic carbenes [2].

Decarboxylation was observed in all tested solvents except water and acids. Thus, the betaine (**2**) is stable in 50% sulphuric acid at 100°C over a period of 2 h, presumably due to protonation to the pyrazolium-3-carboxylic acid (**4**) in solution. The corresponding sulphate or hydrogensulphate of **4**, however, is not isolable in the solid state, as it spontaneously deprotonates to the betaine (**2**). In alcohols, such as ethanol or 1-propanol, and

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halogenated solvents, such as chloroform or dichloromethane, reflux over a period of one hour is necessary to complete the decarboxylation of **2**. In dimethylsulfoxide and *N,N*-dimethylformamide the decarboxylation starts at approximately 60°C and is complete in 2 hours. Only in acetone does the reaction take place at room temperature, and no trace of **2** can be detected by tlc after 2 hours.

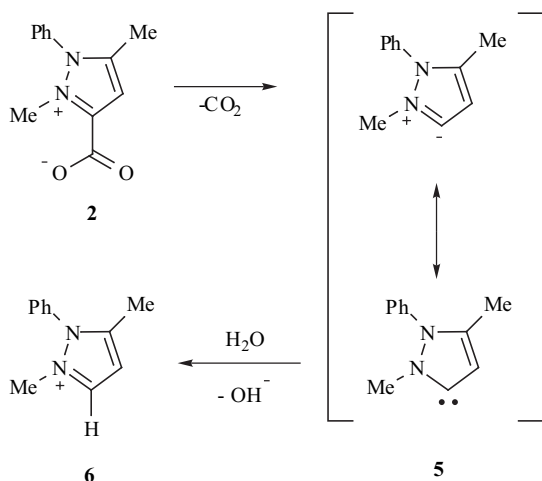


Fig. (2).

The decarboxylation can be monitored by  $^1\text{H}$  NMR spectroscopy at various temperatures. Measurements were carried out in DMF- $d_7$  or DMSO- $d_6$  starting at 20°C. Only traces of the pyrazolium salt (**6**) were detectable in the temperature range between 20°C and 40°C. At 60°C the decarboxylation of the betaine (**2**) started, as indicated by two doublets at  $\delta = 8.86$  ppm ( $^3J = 2.82$  Hz) and at  $\delta = 7.05$  ppm ( $^3J = 2.82$  Hz), respectively, assignable to 3-*H* and 4-*H* of the pyrazolium salt (**6**). Peak assignments are in agreement to measurements of **5** in DMSO- $d_6$ .<sup>1</sup> After 1 hour at 60°C traces of the betaine (**2**) were still detectable, e.g. by the singlet at  $\delta = 6.90$  ppm of 4-*H*. The ratio of **2** to **6** changed from 81 : 19 at the beginning of the measurement at 60°C to 64 : 36 after 1 hour. The water of crystallisation of the betaine (**2**), which stabilises the betaine and could not be removed despite of intense efforts, prevented us from the direct observation of the nucleophilic carbene (**5**). Obviously, it is trapped immediately to form the pyrazolium salt (**6**). This behaviour can be demonstrated by the following reactions.

Nucleophilic carbenes are strong organic bases. The basicity of the *in situ* generated pyrazolium-3-ylidene (**5**) can be demonstrated by dissolving the betaine (**2**) in acetone followed by heating at reflux temperature. This procedure results in the formation of the 4-hydroxy-4-methyl-pentane-2-one (**8**) - which is a known compound [15] - in 94% isolated yield, obviously formed by deprotonation of the acetone ( $pK_a$  20 in water at 25°C) by the carbene (**5**) to the corresponding enolate, followed by aldol addition (Fig. (3)). Reaction of (**2**) with 2,3,4-trimethoxy-benzaldehyde in the

presence of ethyl malonate for 20 min. gives the benzylidene-malonic acid diethyl ester (**9**) in 42% yield as a result of a Knoevenagel reaction. No traces of **2** were detectable after the reaction was completed. The spectroscopic data of **9** are in total agreement to those reported [16].

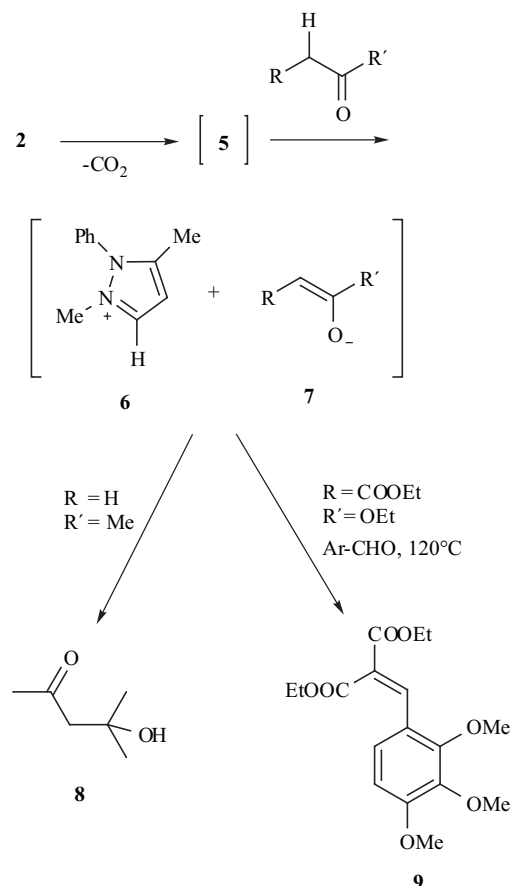


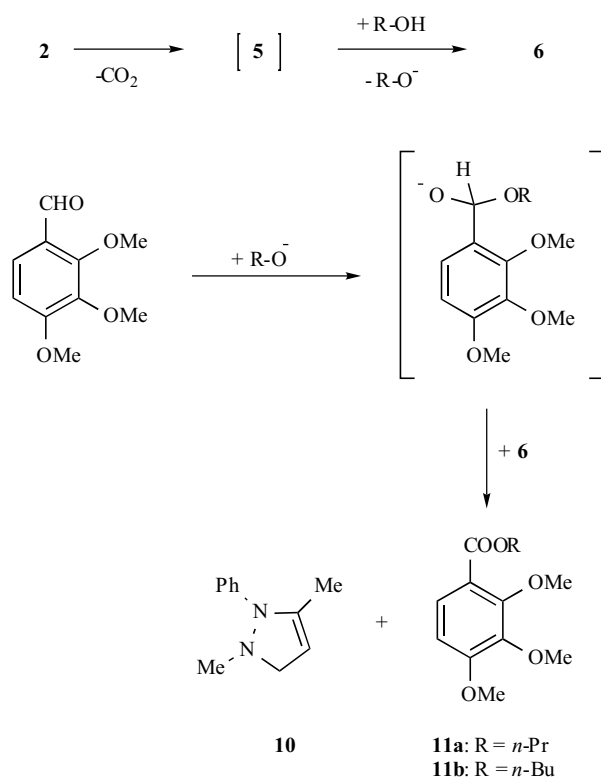
Fig. (3).

Solutions of **2** in 1-propanol and 1-butanol, respectively, react with 2,3,4-trimethoxybenzaldehyde at reflux temperature to give the 2,3,4-trimethoxybenzoic acid esters (**11a**)<sup>2</sup> and (**11b**) in 52% and 43% isolated yield, respectively (Fig. 4). The spectroscopic data of **11b** are identical to the data obtained of a sample prepared by esterification of the corresponding benzoic acid [17]. The reaction described here can be explained by the formation of the nucleophilic carbene (**5**), which deprotonates the alcohols. The resulting alcoholates attack the aldehyde to form an intermediate shown in Fig. (5). Subsequent hydride abstraction results in the formation of the esters (**11a,b**). The hydride may react with the alcohols or the water of crystallisation, forming hydrogen, and with the iminium moiety of the pyrazolium salt (**6**), which gave the known pyrazoline (**10**) [18] in a Leuckart-Wallach-type reaction. We did not observe the formation of benzylic alcohols, so that the aldehyde as hydride acceptor in a Cannizzaro-type

<sup>1</sup>  $^1\text{H}$ NMR-measurements in DMSO- $d_6$  showed two doublets at  $\delta = 8.47$  ( $^3J = 2.91$  Hz) and at  $\delta = 6.85$  ( $^3J = 2.91$  Hz) corresponding to one proton each, two singlets at  $\delta = 3.67$  (N-methyl) and at  $\delta = 2.49$  (methyl) and a multiplett at  $\delta = 7.50 - 7.80$  (phenyl group).

<sup>2</sup> Colorless oil.  $^1\text{H}$ -NMR (200 MHz, 20°C,  $\text{CDCl}_3$ ):  $\delta = 7.61$  (d, 1 H,  $J = 8.84$  Hz); 6.70 (d, 1 H,  $J = 8.84$  Hz); 4.26 (t, 2 H,  $J = 6.63$  Hz); 3.94 (s, 3 H); 3.91 (s, 3 H); 3.88 (s, 3 H); 1.79 (m, 2 H); 1.03 (t, 3 H,  $J = 7.45$  Hz) ppm;  $^{13}\text{C}$ -NMR (50 MHz, 20°C,  $\text{CDCl}_3$ ):  $\delta = 165.7$ ; 157.0; 154.4; 142.9; 126.8; 118.2; 107.0; 66.3; 61.7; 60.9; 56.0; 22.0; 10.3 ppm.

disproportionation was excluded from consideration. Additional experimental work along these lines is in progress.



**Fig. (4).**

#### ACKNOWLEDGEMENTS

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#### REFERENCES

- [1] Arduengo, A. J.; III, Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.*, **1991**, *113*, 361.
- [2] Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.*, **2000**, *100*, 39.
- [3] Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.*, **1998**, *37*, 2490.
- [4] Wanzlick, H. W.; Schönherr, H. J. *Liebigs Ann. Chem.*, **1970**, *731*, 176; Schönherr, H. J.; Wanzlick, H. W. *Chem. Ber.*, **1970**, *103*, 1037.
- [5] Kuhn, N.; Kratz, T. *Synthesis*, **1993**, 561.
- [6] Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.*, **1995**, *34*, 1021.
- [7] Katritzky, A. R.; Faid-Allah, H. M. *Synthesis*, **1983**, 149; Katritzky, A. R.; Awartani, R.; Patel, R. C. *J. Org. Chem.*, **1982**, *47*, 498; Quast, H.; Schmitt, E. *Liebigs Ann. Chem.*, **1970**, *732*, 43; Quast, H.; Schmitt, E. *Justus Liebigs Ann. Chem.*, **1970**, *732*, 64.
- [8] Schmidt, A. *Adv. Heterocycl. Chem.*, **2003**, *85*, 67; Schmidt, A. *Curr. Org. Chem.*, **2004**, *8*, 653; Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron*, **1985**, *41*, 2239.
- [9] Dyson, P.; Hammick, D. L. *J. Chem. Soc.*, **1937**, 1724.
- [10] Kuhn, N.; Steimann, M.; Weyers, G. *Z. Naturforsch.*, **1999**, *54b*, 427; Ishiguro, K.; Hirabayashi, K.; Nojima, T.; Sawaki, Y. *Chem. Lett.*, **2002**, *8*, 796; Holbrey, J. D.; Reichert, W. M.; Tkatchenko, I.; Bouajila, E.; Walter, O.; Tommasi, I.; Rogers, R. D. *Chem. Commun.*, **2003**, *1*, 28.
- [11] Schmidt, A.; Mordhorst, T.; Nieger, M. *Nat. Prod. Res.*, **2004**, in press; Schmidt, A.; Mordhorst, T., *ARKIVOC* **2003**, *XIV*, 233; Schmidt, A.; Gholipour Shilabin, A. *Org. Biomol. Chem.*, **2003**, *1*, 4342; Schmidt, A.; Kindermann, M. K.; Vainiotalo, P.; Nieger, M. *J. Org. Chem.*, **1999**, *64*, 9499.
- [12] Schmidt, A. *J. Heterocycl. Chem.*, **2002**, *39*, 949; Schmidt, A.; Mordhorst, T.; Habeck, T. *Org. Lett.*, **2002**, *4*, 1375; Schmidt, A.; Kindermann, M. K. *J. Org. Chem.*, **1998**, *63*, 4636.
- [13] Schmidt, A.; Habeck, T.; Kindermann, M. K.; Nieger, M. *J. Org. Chem.*, **2003**, *68*, 5977.
- [14] Atta-ur-Rahman; Malik, S.; Cun-heng, H.; Clardy, J. *Tetrahedron Lett.*, **1985**, *26*, 2759.
- [15] Broomhead, E. J.; McLauchlan, K. A.; Roe, J. C. *J. Chem. Soc., Perkin Trans. 2*, **1980**, 796.
- [16] Papadakis, P. E.; Boand, W. *J. Org. Chem.*, **1961**, *26*, 2075.
- [17] Hewgill, F. R.; Slamet, R.; Stewart, J. M. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 3033.
- [18] Elguero, J.; Jacquier, R.; Tizané, D. *Tetrahedron*, **1971**, *123*, 131; Elguero, J. *Bull. Soc. Chim. Fr.*, **1970**, 1121.