ORGANIC
LETTERS

2007
Vol. 9, No. 17
3437−3439

Quinoidal Tetrazines: Formation of a Fascinating Compound Class

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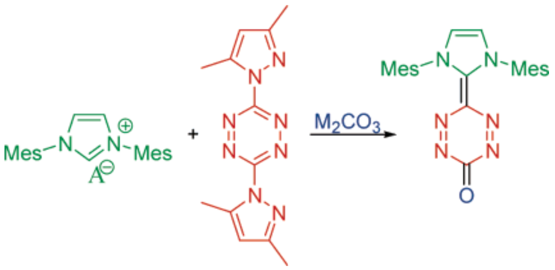
Received June 19, 2007

ABSTRACT



A series of different N-heterocyclic carbenes (NHCs) were reacted with 3,6-bis(3′,5′-dimethylpyrazolyl)-tetrazine in the presence of an inorganic carbonate to provide access to a hitherto unprecedented compound class. The formed tetrazine derivatives bearing the NHC in the 3-position and an oxygen in the 6-position show a quinoidal-like structure, according to physical examinations and X-ray crystallography.

The importance of N-heterocyclic carbenes (NHCs) in organic synthesis has become significant in recent years.[1] Besides their widespread use as ligands in transition-metal-catalyzed processes,[2] the nucleophilic character of stable diaminocarbenes was also an exploited application in organocatalysis.[3] Although NHCs have been used as nucleophiles in multicomponent reactions[4] and in cycloadditions,[5] their potential as reagents in nucleophilic substitutions has been only scarcely explored.[6] Besides the mechanistic relevance, nucleophilic reactions of NHCs with electron-deficient heteroaromatic systems could provide easy access to twisted molecules bearing donor−acceptor substituents, whose intramolecular charge-transfer character has received significant attention recently.[7]

Tetrazines,[8] squeezing four nitrogen atoms into a six-membered ring, are a prime representative of the possible substrates. Heteroatom-based substituents are usually introduced conveniently onto the tetrazine core by nucleophilic substitution,[9] although the incorporation of carbon-based substituents is less trivial.[10] The present communication reports the straightforward synthesis of an unconventional twisted π-electron system by the reaction of nucleophilic carbenes and tetrazines. The unique and unprecedented

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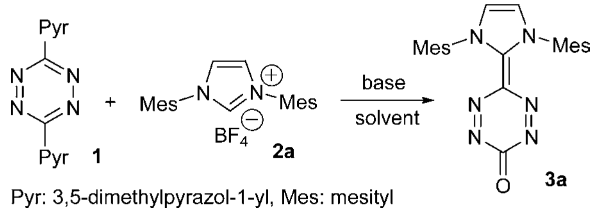
10.1021/ol701442h CCC: $37.00

structure of the products makes them interesting from the synthetic, theoretical, and physical viewpoints alike. Additionally this compound class might also gain application in materials science in the future.

The reaction of the nucleophilic carbene derived from 1,3-dimesityl-imidazolium tetrafluoroborate (**2a**) and dipyrazolyltetrazine (**1**) gave a new compound (**3a**) in excellent yield (Table 1). Spectroscopic investigation of **3a** revealed a so far unprecedented structure, which was confirmed by X-ray crystallography (Figure 1). The C−O bond in **3a** has a strong double bond character (1.235 Å) as compared to the analogous 1,5-dimethyl-3-(3′-pyrazolyl)-6-oxotetrazane, where the C−O bond length is 1.255 Å.[11] The N−N bonds at 1.301 and 1.314 Å are also considerably shorter than the typical data for tetrazines (e.g., 1.330 Å for di(2-pyrimidyl)-tetrazine[12]). These data point to a quinoidal-like structure, although the C1−C11 bond, which was expected to have a double bond character, is quite elongated at 1.46 Å. This might be attributed to the fact that the two heterocyclic rings are tilted by ca. 43°, which should result in a decreased p−p overlap. Such a distortion, although quite rare among organic compounds, might still correspond to a singlet state of a sterically crowded double bond.[13] To rule out the mesomeric zwitterionic form of **3a**, we compared the UV spectra of **3a**, **1**, and di(3-pyridyl)-tetrazine in solvents of different polarity.[14] The obtained $\Delta\lambda_{max}$ values (12, 14, and 12 nm, respectively) do not support the zwitterionic nature of **3a**. This is ruled out both by the X-ray data and by UV measurements.[15]

Table 1. Influence of the Base and Solvent on the Reaction of 3,6-Bis(3′,5′-dimethylpyrazolyl)-tetrazine (**1**) and 1,3-Bis(mesityl)-imidazolium Tetrafluoroborate (**2a**)



Pyr: 3,5-dimethylpyrazol-1-yl, Mes: mesityl

entry	base	solvent	yield
1	NaH	MeCN or THF	−
2	EDIPA or Et_3N	MeCN or THF	traces
3	$NaHCO_3$	MeCN	40%[a]
4	K_2CO_3	DMA	80%[b]
5	K_2CO_3	PhMe	92%
6	K_2CO_3	THF	95%
7	K_2CO_3	MeCN	96% (83%[c])

[a] 5 equiv of $NaHCO_3$, 41 h heating. [b] Na_2CO_3 and Cs_2CO_3 gave **3a** in 80% and 83% yield, respectively. [c] All reagents were mixed at the same time.

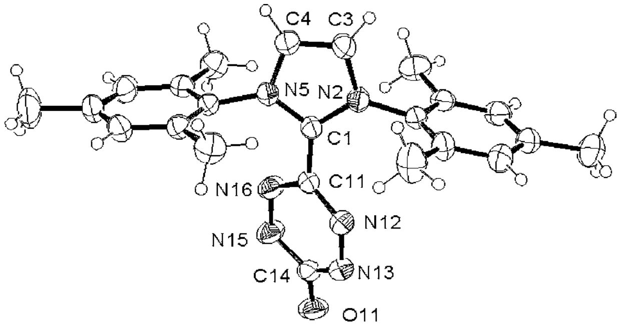


Figure 1. ORTEP diagram of compound **3a** (thermal ellipsoids set at 50% probability) with partial numbering scheme. Selected bond lengths (Å): C1−N2 1.341(4), C1−N5 1.344(4), C3−C4 1.337(4), C14−O11 1.235(4), C14−N13 1.384(5), C14−N15 1.386(4), N12−N13 1.314(4), N15−N16 1.301(4), C11−N12 1.332(4), C11−N16 1.333(4), C1−C11 1.464(4). Torsion angle (deg): N2−C1−C11−N12 43.4.

The presence of a carbonate base was found to be crucial for the formation of **3a** (Table 1, entries 1−3 vs 4−7). These carbonates probably have a dual role in the process: besides generating the carbene, the oxygen atom in the product also originates from this species. The nature of the carbonate and the solvent has only a limited influence on the process because sodium, potassium, and cesium salts were equally efficient (entry 4). The nucleophilicity of the carbonate ion is important in the transformation because using an excess of sodium hydrogencarbonate and prolonged heating (entry 3) we obtained **3a** in poor yield. Of the nonnucleophilic solvents tested, acetonitrile and tetrahydrofurane were chosen for further studies because they combined acceptable solubility and a facile workup. A priori carbene generation was found beneficial (entry 7).

To establish the scope of this transformation, a series of NHC precursors (**2a**−**l**)[16] were reacted with **1** (Table 2).

The experiments[17] revealed that the nature of the carbene backbone has a substantial influence on the efficiency of the process. Reactants based on the imidazole framework were all very efficient, and the products **3a**−**g** were all isolated in good yield (entries 1−7). *N*-Aryl[18] (entries 1 and 2) and *N*-alkyl (entries 3−7) derivatives worked equally well; the

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(11) Wu, J.-Z.; Bouwman, E.; Reedijk, J.; Mills, A. M.; Spek, A. L. *Inorg. Chim. Acta* **2003**, *351*, 326.

(12) Glockle, M.; Hubler, K.; Kummerer, H.-J.; Denninger, G.; Kaim, W. *Inorg. Chem.* **2001**, *40*, 2263.

(13) Sulzbach, H. M.; Bolton, E.; Lenoir, D.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1996**, *118*, 9908.

(14) For details see the Supporting Information.

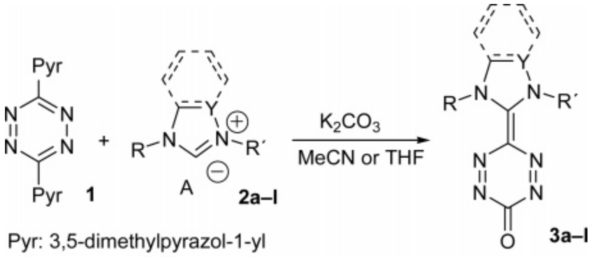
(15) ESR studies on **3a**, **3c**, and **3e** ruled out the presence of any radical character both in solution and in the solid state.

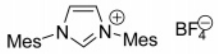
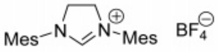
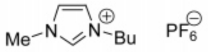
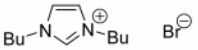
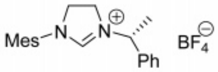
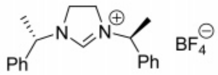
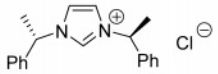
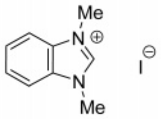
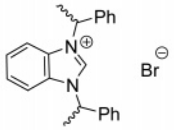
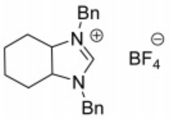
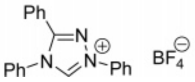
(16) (a) Paczal, A.; Bényei, A. C.; Kotschy, A. *J. Org. Chem.* **2006**, *71*, 5969. (b) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083. (c) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed.* **1995**, *34*, 1021. (d) Herrmann, W. A.; Koecher, C.; Goossen, L. J.; Artus, G. R. J. *Chem.−Eur. J.* **1996**, *2*, 1627.

(17) General procedure: 1 equiv of the carbene precursor (**2a**−**l**) and 1 equiv of K_2CO_3 were stirred in the degassed solvent in a capped vial at 75−80 °C for 40 min under an argon atmosphere. The preheated solution of **1** (1 equiv) in the appropriate solvent was added via cannula, and the mixture was stirred at the same temperature until all starting material was consumed as judged by TLC. After removal of the volatiles in a vacuum, the product was purified by column chromatography on silica gel, using methanol/ethylacetate (1:4) as eluent.

(18) *N*,*N*′-Bis(2,6-diisopropyl-phenyl)-imidazolium salts (IPr) and their dihydro analogue (SIPr) led to the decomposition of **1** without traces of **3**.

Table 2. Formation of Quinoidal Tetrazines from 3,6-Bis(3′,5′-dimethylpyrazolyl)-tetrazine (**1**) and Different Heterocyclic Carbene (NHC) Precursors (**2a−l**)



entry	NHC precursor		yield
1		**2a**	96%[a]
2		**2b**	95%[a]
3		**2c**	99%[a]
4		**2d**	97%[a]
5		**2e**	77%[a]
6		**2f**	90%[a]
7		**2g**	90%[a]
8		**2h**	traces[a,b]
9		**2i**	8%[a] 23%[b]
10		**2j**	52%[a] 49%[b]
11		**2k**	42%[a] traces[b]
12		**2l**	20%[a] 39%[b]

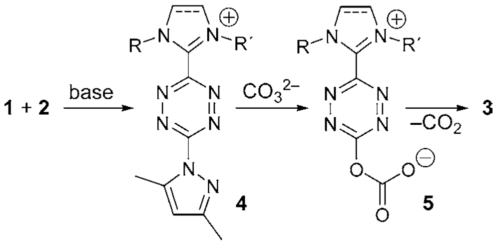
[a] Reaction was carried out in acetonitrile. [b] Reaction was carried out in THF.

optical purity of chiral carbenes was not eroded (entries 5−7), and the partial saturation of the NHC core had no adverse effect on the process (cf. entries 1 and 2, 6 and 7).

The efficiency of NHCs based on the benzimidazole framework (entries 8−11) showed a marked dependence on the nature of the N-substituents. Increasing the steric demand of the substituent led to a marked improvement in the yield (cf. entries 8−10), due probably to the increased stability of the carbene.[19] Partial saturation of the benzimidazole moiety did also increase the yield (cf. entries 9 and 11), as expected on the basis of increased carbene stability. Change of the solvent led to a marked alteration of the yield, although its direction was unpredictable (entries 9 and 11). The triazole-based carbene **2l**[16c] (entry 12) furnished the appropriate tetrazine (**3l**) in moderate yield.

The reaction of NHCs and **1** presumably starts by the nucleophilic displacement of a pyrazole unit in **1** leading to a charged intermediate (**4**), which we were able to detect in the reaction mixture by ESI-MS. Subsequent displacement of the other pyrazole moiety by a carbonate ion leads to the formation of **5**, which on the elimination of carbon dioxide gives the quinoidal tetrazine **2** (Scheme 1).[20]

Scheme 1. Proposed Mechanism for the Substitution



It is interesting to note that Wanzlick carbenes were reported to undergo [4 + 1] cycloaddition with tetrazines,[21] a route we did not observe.

In summary, a variety of structurally unique tetrazine derivatives, having a twisted structure, were prepared using heterocyclic carbenes as nucleophiles. Most of the imidazole-based NHCs gave good to excellent yields, and chirality in the carbene was also transferred into the product. Introduction of other carbene backbones was also possible, although yields became more dependent on the nature of N-substituents. Study of the scope and limitations of this fascinating reaction as well as of the reactivity of the formed quinoidal-like tetrazines is in progress in our laboratory.

Acknowledgment. Financial support through grants OTKA F047125 and KMA-0358/2004 as well as the assistance of Dr. Gitta Schlosser, Mr. Vilibald Kun, Dr. Antal Rockenbauer, and Dr. Gábor Vlád are gratefully acknowledged.

Supporting Information Available: Experimental procedures and structural characterization for compounds **2** and **3** and crystallographic data of **3a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

(20) The reaction of **1** and carbonates does not lead to the displacement of the pyrazole unit, unlike in the case of hydroxides, which give the appropriate substitution product. For details, see ref 8.

(21) Frenzen, G.; Kuemmell, A.; Meyer-Dulheuer, C.; Seitz, G. *Chem. Ber.* **1994**, *127*, 1803.