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A Concise Route to Pyridines from Hydrazides by Metal Carbene N−H Insertion, 1,2,4-Triazine Formation, and Diels−Alder Reaction

Baolu Shi,[†] William Lewis,[†] Ian B. Campbell,[‡] and Christopher J. Moody*,[†]

School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, U.K., and GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, U.K.

c.j.moody@nottingham.ac.uk

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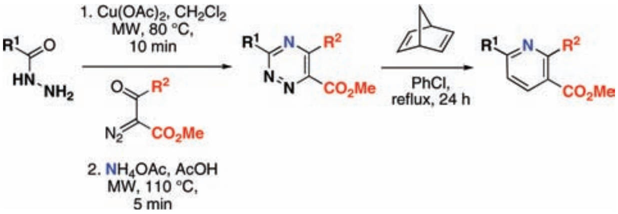
ABSTRACT



A simple, new three-step sequence for the conversion of hydrazides into pyridines is reported in which the key steps are N−H insertion by a copper carbene intermediate derived from α-diazo-β-ketoesters into the hydrazide, reaction with ammonium acetate to give 1,2,4-triazines, followed by Diels−Alder reaction with norbornadiene.

1,2,4-Triazines are a well-known class of nitrogen heterocycles with a range of applications,[1] particularly in the pharmaceutical arena where they can be regarded as azapyrimidines, and hence have given rise to a large number of aza- nucleotides and -nucleosides.[2,3] From a chemical perspective, one of the most useful properties of 1,2,4-triazines is their ability to act as 2-azadienes in the hetero-Diels−Alder reaction.[4−6] This reaction, which is usually an inverse electron demand Diels−Alder reaction, results in addition of an electron-rich dienophile across C3−C6 of the triazine to give, after extrusion of nitrogen from the initial adduct, pyridines in synthetically useful yields.[7−12] We now report a new route to 1,2,4-triazines based on the N−H insertion reactions of carbene intermediates into hydrazides.

One of the most useful synthetic methodologies to emerge in the past two decades involves the transition-metal-catalyzed reactions of diazocarbonyl compounds.[13,14] Our own contributions have focused on the synthesis of nitrogen heterocycles using carbene N−H insertion reactions as key steps. Thus we previously reported the rhodium carbene

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[†] University of Nottingham.
[‡] GlaxoSmithKline.
(1) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry II*; Boulton, A. J., Ed.; Pergamon: Oxford. 1996; Vol. 6, p 507.
(2) Seela, F.; He, Y. *J. Org. Chem.* **2003**, *68*, 367.
(3) Seela, F.; Chittepu, P. *J. Org. Chem.* **2007**, *72*, 4358.
(4) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Vol. 47.
(5) Barluenga, J.; Tomas, M. *Adv. Heterocycl. Chem.* **1993**, *57*, 1.
(6) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1.
(7) For recent examples, see refs 7−12; Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron Lett.* **2002**, *43*, 6015.
(8) Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron* **2004**, *60*, 8893.
(9) Raw, S. A.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **2004**, 508.
(10) Raw, S. A.; Taylor, R. J. K. *J. Am. Chem. Soc.* **2004**, *126*, 12260.
(11) Sainz, Y. F.; Raw, S. A.; Taylor, R. J. K. *J. Org. Chem.* **2005**, *70*, 10086.
(12) Catozzi, N.; Wasnaire, P.; Taylor, R. J. K. *Tetrahedron Lett.* **2008**, *49*, 2865.
(13) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley: New York, 1998.
(14) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577.

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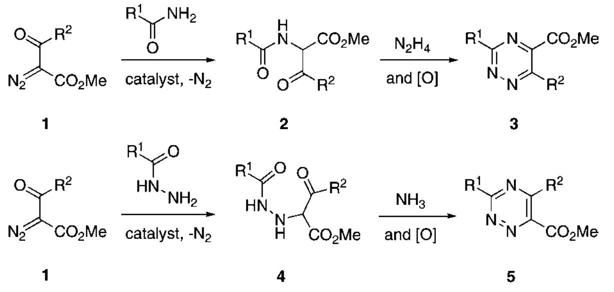
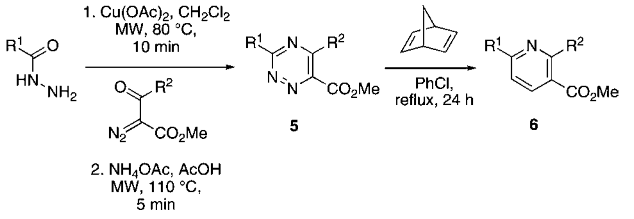
Scheme 1. Possible Carbene N−H Insertion Routes to 1,2,4-Triazines



insertion reaction into the N−H bond of *N*-alkylanilines as a key step in a modified Bischler synthesis of indoles,[15,16] while subsequently Janda and co-workers have developed a solid-phase variant of this reaction.[17] Similarly we have shown that a range of carboxamides undergo dirhodium(II)-catalyzed reaction with α-diazo-*β*-ketoesters to give 1,4-dicarbonyl compounds, readily converted into oxazoles or thiazoles by dehydration or thionation, respectively.[18,19] The reaction has subsequently been applied in the synthesis of the oxazole building blocks of a range of natural products,[20−29] and also has been adapted to solid phase.[30,31] Therefore we were attracted to the idea of using carbene N−H insertion as a simple route to 1,2,4-triazines. Two routes were considered, both starting from a readily available α-diazo-*β*-ketoester **1** (Scheme 1). The first involves the familiar insertion into a carboxamide N−H followed by reaction of the product **2** with hydrazine and aromatization to give the 1,2,4-triazine-5-carboxylate **3**, whereas the second uses hydrazides as the N−H insertion partner, followed by reaction of the intermediate **4** with ammonia and aromatization leading to the isomeric triazine-6-carboxylate **5**. We now report the realization of this second strategy, which when followed by a Diels−Alder reaction with norbornadiene constitutes a new, simple three-step route from hydrazides to pyridines.

Scheme 2. Conversion of Hydrazides into 1,2,4-Triazines **5** and Subsequent Diels−Alder Reaction with Norbornadiene To Give Pyridines **6**



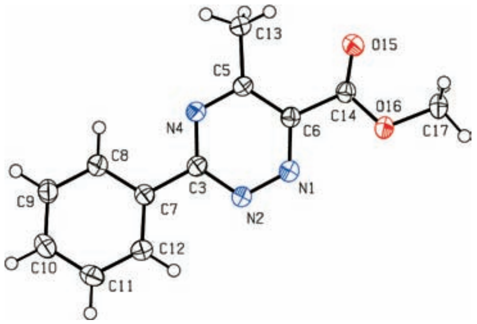


Figure 1. X-ray crystal structure of methyl 5-methyl-3-phenyl-1,2,4-triazine-6-carboxylate **5a**.

Although a range of N−H compounds (amines, anilines, amides, carbamates, ureas) have been reported to participate in carbene N−H insertion reactions, as far as we are aware there have been no accounts describing such reactions with hydrazides. Using benzhydrazide as a model substrate with methyl 2-diazo-3-oxobutanoate as the diazocarbonyl component, we quickly established that copper(II) acetate was the catalyst of choice and that the reaction was most conveniently carried out in a microwave reactor. The product was then treated with ammonium acetate in acetic acid to give after chromatography the 1,2,4-triazine **5a** in modest yield. The nature of the intermediate in this process remains unknown, although we speculate that the initial product of N−H insertion (compound **4** in Scheme 1) is readily oxidized in the presence of copper(II) and air, and it is the resulting azo compound (or more likely its hydrazone tautomer) that subsequently reacts with ammonia to give the aromatic triazine **5a** directly. Indeed treatment of related acylhydrazones with ammonium acetate is known to give 1,2,4-triazines.[32,33] Alternatively, the product of N−H insertion (1,5-dicarbonyl compound **4**) condenses with ammonia, and

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(15) Moody, C. J.; Swann, E. *Synlett* **1998**, 135.

(16) Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J.; Muthusamy, S.; Swann, E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1672.

(17) Lee, S. H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *J. Comb. Chem.* **2003**, *5*, 188.

(18) Bagley, M. C.; Buck, R. T.; Hind, S. L.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 591.

(19) Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron* **2004**, *60*, 3967.

(20) Moody, C. J.; Bagley, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 601.

(21) Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem.* **2005**, *70*, 5840.

(22) Bagley, M. C.; Hind, S. L.; Moody, C. J. *Tetrahedron Lett.* **2000**, *41*, 6897.

(23) Bagley, M. C.; Moody, C. J.; Pepper, A. G. *Tetrahedron Lett.* **2000**, *41*, 6901.

(24) Davies, J. R.; Kane, P. D.; Moody, C. J. *J. Org. Chem.* **2005**, *70*, 7305.

(25) Palmer, F. N.; Lach, F.; Poriel, C.; Pepper, A. G.; Bagley, M. C.; Slawin, A. M. Z.; Moody, C. J. *Org. Biomol. Chem.* **2005**, *3*, 3805.

(26) Lachia, M.; Moody, C. J. *Nat. Prod. Rep* **2008**, *25*, 227.

(27) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301.

(28) Hughes, R. A.; Thompson, S. P.; Alcaraz, L.; Moody, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 15644.

(29) Linder, J.; Blake, A. J.; Moody, C. J. *Org. Biomol. Chem.* **2008**, *6*, 3908.

(30) Clapham, B.; Spanka, C.; Janda, K. D. *Org. Lett.* **2001**, *3*, 2173.

(31) Clapham, B.; Lee, S. H.; Koch, G.; Zimmermann, J.; Janda, K. D. *Tetrahedron Lett.* **2002**, *43*, 5407.

(32) Konno, S.; Sagi, M.; Takaharu, E.; Fujimura, S.; Hayashi, K.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1721.

(33) Ohsumi, T.; Neunhoeffer, H. *Tetrahedron* **1992**, *48*, 651.

Table 1. Conversion of Hydrazides into 1,2,4-Triazines **5** and Subsequent Diels−Alder Reaction with Norbornadiene To Give Pyridines **6**

R^1	R^2	**5**	yield (%)	**6**	yield (%)
Ph	Me	**5a**	43	**6a**	91
2-MeC_6H_4	Me	**5b**	35	**6b**	40
4-$MeOC_6H_4$	Me	**5c**	43	**6c**	52
4-$NO_2C_6H_4$	Me	**5d**	32	**6d**	80
4-BrC_6H_4	Me	**5e**	38	**6e**	87
2-Furyl	Me	**5f**	38	**6f**	45
4-Pyridyl	Me	**5g**	28	**6g**	90
Ph	4-FC_6H_4	**5h**	58	**6h**	94

the resulting dihydrotriazine is readily oxidized/aromatized in air.

The structure of triazine **5a** was confirmed by X-ray crystallography (Figure 1), and subsequently a range of substituted benzhydrazides were converted into 1,2,4-triazines **5b**−**5h** (Table 1). With a range of 1,2,4-triazines in hand, their conversion into pyridines by a hetero-Diels−Alder reaction was investigated using norbornadiene as an ethyne equivalent as the dienophile.[7,8,34−36] The reaction was carried out by heating the triazine **5** with an excess of norbornadiene in boiling chlorobenzene for several hours and gave the pyridines **6** in modest to excellent yield (Table 1).

In conclusion, we have developed a new, simple route to pyridines from readily available hydrazides by way of 1,2,4-triazines. This three-step process illustrates the power and versatility of transition-metal mediated carbene N−H insertion reactions in organic synthesis, and in particular the synthesis of important heterocyclic compounds.

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Supporting Information Available: Full experimental details, copies of ^1H and ^{13}C NMR spectra of compounds **5** and **6**, and cif file for X-ray crystal structure of compound **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) For other examples of use of norbornadiene, see refs 34−36; Barlow, M. G.; Haszeldine, R. N.; Simpkin, D. J. *J. Chem. Soc., Chem. Commun.* **1979**, 658.

(35) Pabst, G. R.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 6687.

(36) Altuna-Urquijo, M.; Gehre, A.; Stanforth, S. P.; Tarbit, B. *Tetrahedron* **2009**, *65*, 975.