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SYNTHESIS OF FUSED PYRIDINES BY ELECTROCYCLIC RING CLOSURE OF ALDEHYDE *NN*-DIMETHYLHYDRAZONES

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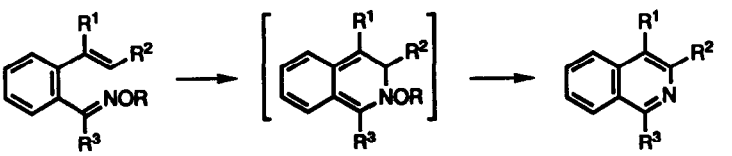
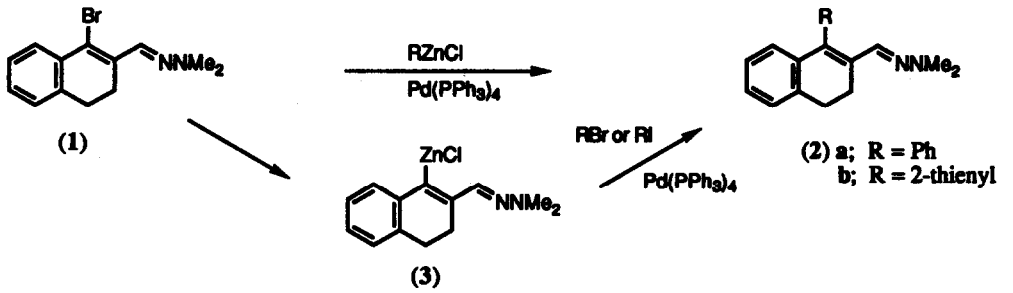
Summary: 3,4-Dihydronaphthalene-2-carboxaldehyde NN-dimethylhydrazones bearing an alkenyl or aryl substituent at the 1-position undergo thermal electrocyclic ring closure followed by the loss of dimethylamine, giving fused pyridines.

Until recently there have been few useful examples of thermal electrocyclic ring closure of 1-azatrienes. Most of the reactions of this type which have been reported involve the reversible ring opening of pyridinium salts by nucleophiles.[1] An exception is the formation of isoquinolines from suitably substituted *o*- quinodimethanes which was explored by Oppolzer and by Kametani and their co-workers in the 1970's.[2] In the last two or three years several other examples of isoquinoline synthesis have been reported which are based on the electrocyclic ring closure of aromatic oximes or oxime ethers (Scheme 1).[3] In addition, Okamura and his co-workers have described examples of electrocyclization of *N*- alkylazatrienes derived from retinal.[4]



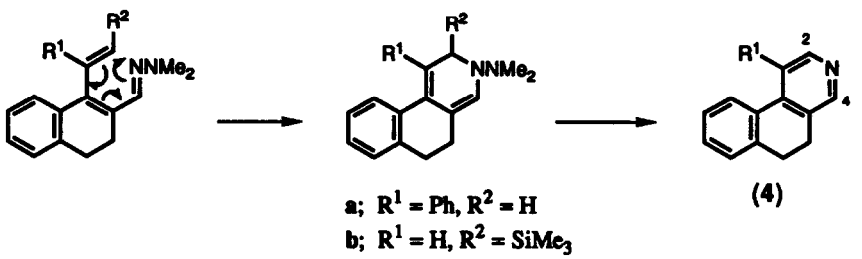
Scheme 1

We have made use of palladium(0) catalysed cross-coupling reactions to prepare trienes suitable for electrocyclic ring closure.[5] In order to explore the viability of the 1-azatriene cyclization as a route to pyridines and dihydropyridines we have adapted this chemistry to prepare a series of model systems derived from 1-bromo-3,4-dihydronaphthalene-2-carboxaldehyde, a precursor which is readily available from 1-tetralone.[5a] The aldehyde was converted into its *NN*- dimethylhydrazone (1). This hydrazone was then coupled to a series of aryl and vinyl halides by one of two procedures (Scheme 2). Reaction with phenylzinc chloride or with 2-thienylzinc chloride in the presence of $Pd(PPh_3)_4$ gave respectively the 1-phenyl and 1-(2-thienyl) compounds (2a) (41%) and (2b) (85%). It was found that compound (2a) could be obtained in better yield (79%) by inverse coupling of the organozinc intermediate (3) with iodobenzene. The organozinc species (3) was generated from the bromonaphthalene (1) by reaction with t-butyllithium followed by the addition of zinc chloride.[6]



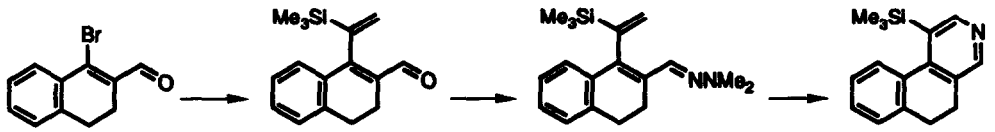
Scheme 2

This latter coupling method also proved to be the more efficient for the introduction of vinyl substituents at the 1-position. Coupling reactions were carried out using α-bromostyrene and (2-bromovinyl)trimethylsilane. In each case a major product was isolated which proved not to be the expected 1-substituted 2-carboxaldehyde dimethylhydrazone. Instead, the products were identified as the pyridines (4) resulting from cyclization of the hydrazones and aromatization. Evidently these cyclizations occurred under the conditions used to carry out the coupling reactions (tetrahydrofuran at 67°C). The structure (4a) was assigned to the product derived from α-bromostyrene on the basis of its spectra;[7] the benzisoquinoline (4b) is a known compound.[8] The loss of the trimethylsilyl group in the aromatization step presumably occurs in preference to loss of a proton and elimination of dimethylamine (Scheme 3).



Scheme 3

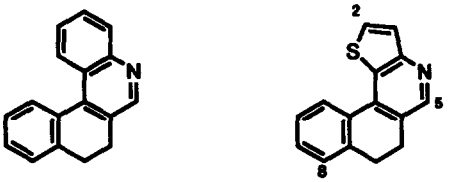
We wished to determine whether the easy cyclization which occurred in this last reaction would be influenced by the position of the trimethylsilyl group; that is, whether the cyclization would also take place readily with a (1-vinyl)trimethylsilyl substituent. We have found previously that coupling reactions of this type in which (1-bromovinyl)trimethylsilane is the electrophile are not regioselective.[9] The coupled product was therefore obtained in a different way. 1-Bromo-3,4-dihydronaphthalene-2-carboxaldehyde reacted with (1-vinyl)trimethylsilylzinc chloride to give the 1-substituted aldehyde (5) (Scheme 4). This aldehyde, when heated in toluene with 1,1-dimethylhydrazine, gave the benzisoquinoline (4c)[10] directly. Thus, the electrocyclizations appear to take place under remarkably mild conditions and they are not dependent upon the electronic or steric influences of a trimethylsilyl group on the terminal double bond of the azatriene.



(5) (4c)

Scheme 4

Even the 1-arylhydrazones (2a) and (2b) were found to cyclize under more vigorous conditions. The compounds slowly cyclized in the melt, but cyclization was achieved more effiiciently on a small scale by subjecting the hydrazones to vacuum pyrolysis at 650°C and 10^{-2} mmHg. The hydrazone (2a) gave the known[11] benzophenanthridine (6) and (2b) gave the analogous thienoisoquinoline (7)[12], both in fairly good yield. We were surprised to find that these cyclizations took place in preference to intramolecular electrophilic substitution or to elimination of dimethylamine from the aldehyde dimethylhydrazones to give the corresponding nitriles.[13]



(6) (7)

These results lead us to conclude that dimethylhydrazones are useful alternatives to oximes or oxime ethers for electrocyclic reactions leading to the formation of pyridine rings, and that the scope of the reaction may be considerable.

Acknowledgements. We thank the S.E.R.C. for a Research Studentship (M.A.M.H) and the S.E.R.C High Field NMR Service, University of Warwick, for the 400 MHz spectrum of (7).

References and notes

1 Marvell, E. N. *Thermal Electrocyclic Reactions,* Academic Press, New York, 1980.

2 Kametani, T.; Takahashi, T.; Ogasawara, K.; Fukumoto, K. *Tetrahedron*, 1974, **30**, 1047; Kametani, T.; Takemura, M.; Ogasawara, K.; Fukumoto, K. *J. Heterocycl. Chem.*, 1974, **11**, 179; Oppolzer, W.; Petrzilka, M.; Bättig, K. *Helv. Chim. Acta*, 1977, **60**, 2964; Shishido, K.; Hiroya, K.; Fukumoto, K. *Heterocycles*, 1989, **28**, 39.

[3] Hibino, S.; Sugino, E.; Choshi, T.; Sato, K. *J. Chem. Soc., Perkin Trans. 1*, 1988, 2429; Hibino, S.; Sugino, E.; Adachi, Y.; Nomi, K.; Sato, K. *Heterocycles*, 1989, **28**, 275; Hibino, S.; Sugino, E.; Ogura, N.; Shintani, Y.; Sato, K. *Heterocycles*, 1990, **30**, 271.

[4] Okamura, W. H.; de Lera, A. R.; Reischl, W. *J. Am. Chem. Soc.*, 1988, **110**, 4462; de Lera, A. R.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.*, 1989, **111**, 4051; see also Girling, R.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1*, 1988, 1317.

[5] (a) Gilchrist, T. L.; Summersell, R. J. *J. Chem. Soc., Perkin Trans. 1*, 1988, 2595; (b) Gilchrist, T. L.; Summersell, R. J. *J. Chem. Soc., Perkin Trans. 1*, 1988, 2603.

[6] Bromine-lithium exchange can also be achieved using butylllithium at -78°C (this is in contrast to the reaction of aromatic aldoxime ethers with butyllithium, in which reaction occurs at the aldoxime function: Itsuno S.; Miyazaki, K.; Ito, K. *Tetrahedron Lett.*, 1986, **27**, 3033).

[7] (**4a**) (35%), m.p. 141-143°C; δ (200 MHz) 2.78-2.95 (4 H, m), 6.85-6.89 (2 H, m), 7.11-7.42 (5 H, m), 7.59-7.70 (2 H, m), 8.43 (1 H, s) and 8.48 (1 H, s) (H-2 and H-4); picrate m.p. 178-180°C.

[8] Herz, W.; Murty, D. R. K. *J. Org. Chem.*, 1961, **26**, 418. Picrate of (**4b**) m.p. 211-213°C (lit. 210-211°C).

[9] Ennis, D. S.; Gilchrist, T. L. *Tetrahedron*, 1990, **46**, 2623.

[10] (**4c**) (55%), m.p. 94-96°C; δ (200MHz) 0.32 (9 H, s, $SiMe_3$), 2.71-2.87 (4H, m), 7.26-7.36 (3H, m), 7.63-7.68 (1H, m, H-10), 8.46 (1H, s) and 8.70 (1H, s) (H-2 and H-4). Compound (**4c**) was also isolated (68%) when the aldehyde was treated in ethanol with hydroxylamine: the oxime thus also cyclises readily.

[11] Ricci, A.; Balucani, D. *Gazz. Chim. Ital.*, 1977, **107**, 19. Picrate of (**6**) m.p. 268-270°C (lit. 270°C).

[12] (**7**) (68%), oil; δ (400 MHz) 2.89-2.93 (2 H, m), 2.96-3.00 (2 H, m), 7.35 (1 H, dd, *J* 7.5 and 2.0 Hz, H-8), 7.37 (1 H, ddd, *J* 7.5, 7.0, and 1.0 Hz, H-9), 7.45 (1 H, ddd, *J* 7.5, 7.0, and 2.0 Hz, H-10), 7.60 (1 H, d, *J* 5.6 Hz, H-2), 7.72 (1 H, d, *J* 5.6 Hz, H-3), 8.27 (1 H, dd, *J* 7.5 and 1.0 Hz, H-11), and 8.61 (1 H, s, H-5); picrate m.p. 234-236°C.

[13] One possibility is that the preference for cyclisation over elimination to the nitrile is a consequence of the configuration of the hydrazone (presumably *E* in these cases).

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