Pergamon

Tetrahedron Letters 43 (2002) 6015–6017

TETRAHEDRON LETTERS

Synthesis of pyridine derivatives using aza Diels–Alder methodology

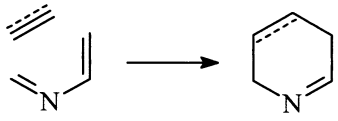
Stephen P. Stanforth,[a,*] Brian Tarbit[b] and Michael D. Watson[a]

[a]*School of Applied and Molecular Sciences, University of Northumbria, Newcastle-upon-Tyne NE1 8ST, UK*
[b]*Seal Sands Chemicals Ltd., Seal Sands Road, Seal Sands, Middlesbrough TS2 1UB, UK*

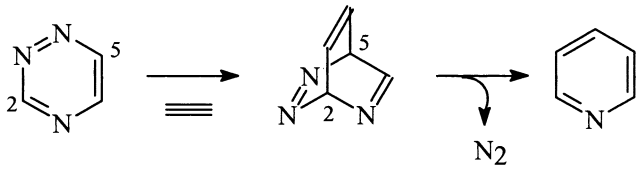
Received 21 May 2002; revised 20 June 2002; accepted 24 June 2002

Abstract—Amidrazone **1** reacted with the unsymmetrical tricarbonyls **2a**, **2c** and **2d** giving triazines **3a**, **3c** and **3d**, respectively. These triazines were converted into their corresponding pyridine derivatives **6a**, **6c** and **6d** in aza Diels–Alder reactions with 2,5-norbornadiene **5**. Triazines **3c** and **3d** gave the pyridolactones **9c** and **9d** with 2,3-dihydrofuran.

The aza Diels–Alder reaction as generalised in Scheme 1 has become an important synthetic route to pyridines and several recent reviews discuss the scope and application of this versatile methodology.[1] In this reaction, a 2-azadiene reacts with a suitable dienophile to form a dihydro or tetrahydropyridine derivative. A diverse range of 2-azadienes and dienophiles have been utilised in this reaction enabling the preparation of a wide variety of pyridine derivatives. 1,2,4-Triazines[2] have been used on many occasions as 2-azadiene equivalents and these heterocycles can react with suitable acetylene equivalents yielding pyridines (Scheme 2).



Scheme 1.



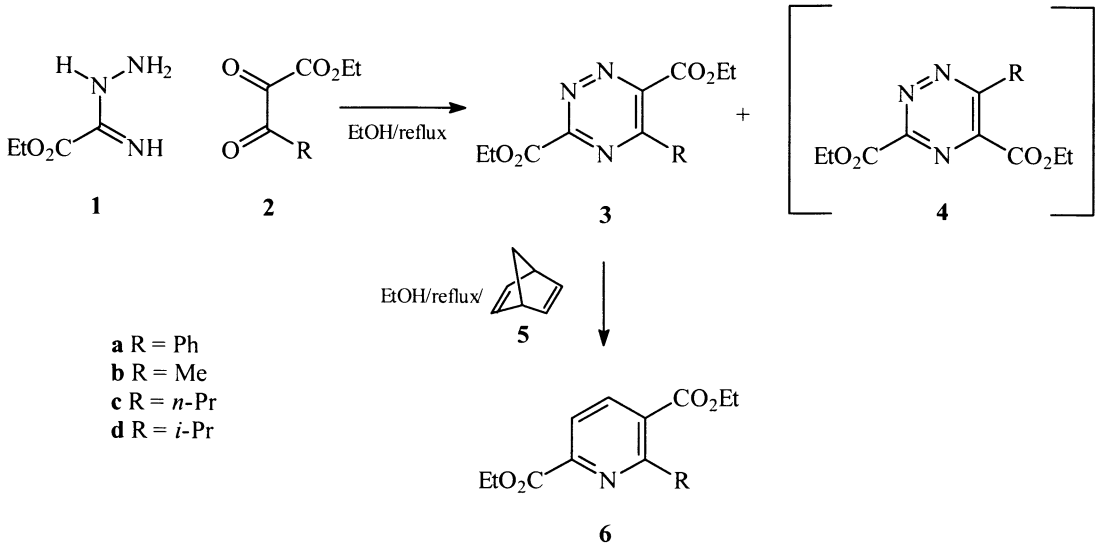
Scheme 2.

We have been interested in preparing pyridine derivatives **6** using the aza Diels–Alder reaction of 1,2,4-triazines derivatives **3** with 2,5-norbornadiene **5** as an acetylene equivalent (Scheme 3).[3] The triazine derivatives **3** which we required would be available from the condensation[2] of amidrazone **1** with the tricarbonyl derivatives **2** (the central carbonyl groups of compounds **2** are hydrated but their keto forms are shown for simplicity). Interestingly, only a few examples of the reaction of amidrazones with *unsymmetrical* tricarbonyl compounds have been reported. Thus, the amidrazone $PhC(=NH)NHNH_2$ and compound **2a** gave only ethyl 3,5-diphenyl[1,2,4]triazine-6-carboxylate (70%)[4] whereas the same amidrazone and compound **2b** gave a mixture of triazines (which were derived from attack of the hydrazine moiety of the amidrazone at each of the keto-carbonyl groups of compound **2b**) in unspecified yields.[5] The reaction of amidrazone **1** with tricarbonyl **2b** was examined by Snyder and co-workers who obtained a 10.5:1 mixture of triazines **3b** and **4b** in 46% yield.[6] Consequently, we envisaged that the reaction of amidrazone **1**[7] and unsymmetrical tricarbonyls **2**[8] might be developed as a useful method for the synthesis of novel pyridine derivatives via triazine intermediates.

Amidrazone **1** and compound **2a** reacted to give a single triazine derivative, compound **3a** (82%). When compound **3a** was heated in ethanol at reflux in the presence of 2,5-norbornadiene **5**, the pyridine derivative **6a** was formed in 84% yield. The structure of compound **6a** was established by hydrolysis (EtOH/KOH/reflux) of the less sterically crowded 6-ester substituent and decarboxylation of the resulting carboxylic acid yielding the known ethyl 2-phenylpyridine-3-carboxyl-

Keywords: aza Diels–Alder reaction; aza dienes; triazines; pyridines.
* Corresponding author. Tel.: 0191 2274784; fax: 0191 2273519; e-mail: steven.stanforth@unn.ac.uk

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01215-7



1 2 3 4 5 6

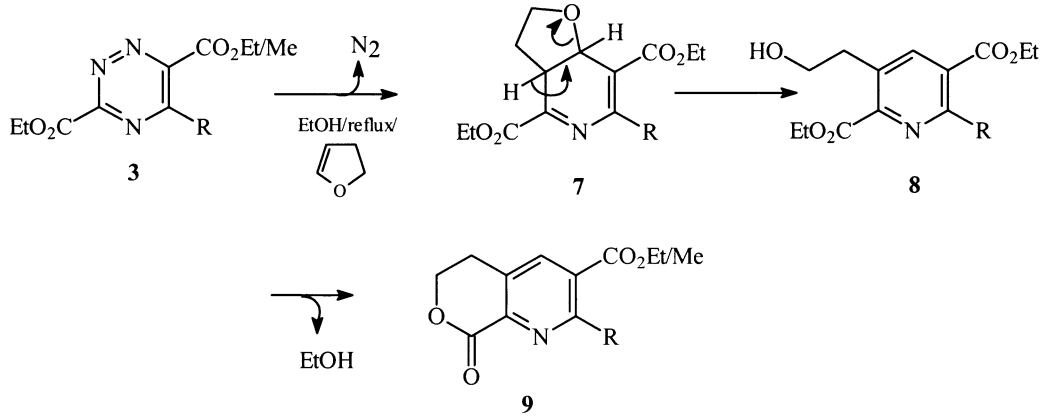
Scheme 3.

ate.[9] The condensation reaction of compounds **1** and **2a** must have therefore yielded triazine **3a** and not the isomeric triazine **4a**. Pyridine **6a** could also be prepared in a 'one-pot' reaction in 59% without the isolation of triazine **3a**. Thus, after compounds **1** and **2a** had been heated in ethanol, 2,5-norbornadiene **5** was added and heating was continued giving pyridine derivative **6a** directly.

Amidrazone **1** and compound **2b** gave a 7:3 mixture of triazines **3b** and **4b** (95%) by ^{1}H NMR spectroscopy confirming Snyder's observations.[6] We therefore decided to investigate the effect of larger alkyl substituents and the isomers **2c** and **2d** were chosen for study. Pleasingly, both compounds **2c** and **2d** reacted with amidrazone **1** giving the triazine derivatives **3c** and **3d**, respectively, in yields exceeding 90%. In view of the simplicity of the 'one-pot' synthesis of pyridine **6a** noted above, pyridine derivatives **6c** (78%) and **6d** (72%) were both prepared using similar reactions.

2,3-Dihydrofuran has been used by Gilchrist and coworkers[10] as an acetylene equivalent in the aza Diels–Alder reaction of triazines. Compounds **3c** and **3d** reacted with 2,3-dihydrofuran in ethanol at reflux in a 'one-pot' reaction yielding the lactones **9c** and **9d**, respectively, in moderate yields (both 44%) as shown in Scheme 4. Only one product was isolated from these reactions indicating the cycloaddition reactions giving intermediates **7c** and **7d** were regioselective. Ring-opening of the ether ring in compounds **7c** and **7d** then yielded the pyridine intermediates **8c** and **8d** which could not be isolated but underwent lactonisation giving the products **9c** and **9d**. The proposed regioselectivity depicted in formula **7** was confirmed by preparing the mixed ester **3c** (C5-ester = methyl ester). Reaction of this compound with 2,3-dihydrofuran gave compound **9** (ester = methyl ester) indicating that the 2-ester substituent in triazine **3c** is involved in lactonisation.

We have shown that amidrazone **1** reacts with unsymmetrical tricarbonyl derivatives **2a**, **2c** and **2d** giving single triazine products **3a**, **3c** and **3d**, respectively. These triazines, can readily be converted into pyridine derivatives by reaction with 2,5-norbornadiene **5** or 2,3-dihydrofuran under mild conditions. All new pyridine derivatives gave satisfactory spectral and microanalytical data and/or high-resolution mass spectra.



3 7 8 9

Scheme 4.

Acknowledgements

We thank Seal Sands Chemicals Ltd. for generous financial support and the EPSRC mass spectrometry service for high-resolution mass spectra.

References

1. For recent aza Diels–Alder reviews, see: (a) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259–5288; (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138; (c) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471.
2. Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, Chapter 6.11, pp. 507–573.
3. For recent examples of 2,5-norbornadiene/1,2,4-triazine cycloadditions, see: (a) Pabst, G. R.; Sauer, J. *Tetrahedron Lett*. **1998**, *39*, 6687–6690; (b) Pabst, G. R.; Schmid, K.; Sauer, J. *Tetrahedron Lett*. **1998**, *39*, 6691–6694; (c) Pabst, G. R.; Sauer, J. *Tetrahedron Lett*. **1998**, *39*, 8817–8820; (d) Pfuller, O. C.; Sauer, J. *Tetrahedron Lett*. **1998**, *39*, 8821–8824; (e) Pabst, G. R.; Pfuller, O. C.; Sauer, J. *Tetrahedron Lett*. **1998**, *39*, 8825–8828.
4. Sagi, M.; Wada, K.; Konno, S.; Yamanaka, H. *Heterocycles* **1990**, *30*, 1009–1021.
5. Ohsumi, T.; Neunhoeffer, H. *Tetrahedron* **1992**, *48*, 651–662.
6. (a) Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem*. **1990**, *55*, 3257–3269. Compound **6b** has also been obtained as a by-product of a Bohlmann–Rahtz reaction, see: (b) Bagley, M. C.; Dale, J. W.; Hughes, D. D.; Ohnesorge, M.; Phillips, N. G.; Bower, J. *Synlett* **2001**, 1523–1526.
7. Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem*. **1994**, *59*, 2623–2625.
8. Tricarbonyls **2a**–**d** were prepared from their commercially available 1,3-dicarbonyl precursors ($RCOCH_2CO_2Et$) by diazo-transfer reactions giving the diazo-compounds [$RCOC(N_2)CO_2Et$] and then treatment of these diazo-compounds with ^{t}BuOCl. For example, see: Detering, J.; Martin, H.-D. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*, 695–698.
9. Yamauchi, M.; Shirota, M.; Tsugane, A. *J. Heterocyclic Chem*. **1997**, *34*, 93–96.
10. Rocha Gonsalves, A. M. d'A.; Pinho e Melo, T. M. V. D.; Gilchrist, T. L. *Tetrahedron* **1993**, *49*, 5277–5290.