Tetrahedron Letters 49 (2008) 4720–4721

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A convenient synthesis of substituted 2,2′:6′,2″-terpyridines

Alexander Gehre [a], Stephen P. Stanforth [a,*], Brian Tarbit [b]

[a] School of Applied Sciences, Northumbria University, Newcastle upon Tyne NE1 8ST, UK
[b] Vertellus Specialities Chemicals UK Ltd, Seal Sands Road, Seal Sands, Middlesbrough TS2 1UB, UK

ARTICLE INFO

Article history:
Received 11 April 2008
Revised 15 May 2008
Accepted 28 May 2008
Available online 2 June 2008

Keywords:
2,2′:6′,2″-Terpyridines
Aza Diels–Alder reaction
1,2,4-Triazines

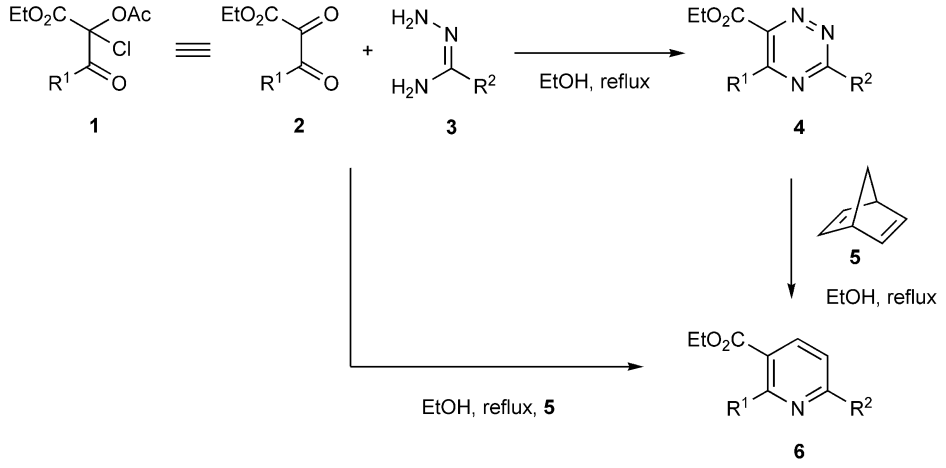
ABSTRACT

The 2,2′:6′,2″-terpyridines **8a** and **8b** were prepared in good yield by reacting α-acetoxy-α-chloro-β-keto-esters **1** (R^1 = ^{n}Pr and Ph) with the bis-amidrazone **7** and 2,5-norbornadiene **5** in ethanol at reflux.

2,2′:6′,2″-Terpyridines have found extensive use in both coordination chemistry and supramolecular chemistry, and consequently synthetic approaches to this important class of ligand have attracted considerable attention.[1] We have previously described a convenient methodology that has enabled the preparation of 2,2′-bipyridine derivatives,[2–6] and in this Letter we disclose how this work has been extended and adapted to allow the synthesis of 2,2′:6′,2″-terpyridines.

We have demonstrated that readily available α-acetoxy-α-chloro-β-keto-esters **1** are synthetic equivalents of α,β-diketo-esters **2**,[5] which reacted with amidrazones **3** yielding triazines **4**. An aza Diels–Alder reaction of these triazines using 2,5-norbornadiene **5** as an acetylene equivalent (or with other aza dienophiles)[5,6] furnished pyridine derivatives **6** (Scheme 1). The substituted pyridines **6** could also be produced in a 'one-pot' reaction directly from compounds **1**, amidrazones **3** and 2,5-norbornadiene **5** in ethanol solution at reflux without isolating the triazines **4**. When the amidrazone **3** had R^2 = 2-pyridyl, then 2,2′-bipyridines were formed.

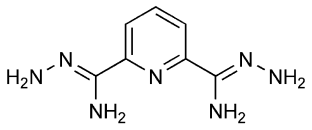
When the bis-amidrazone **7** (available from the reaction of 2,6-dicyanopyridine with hydrazine)[7] was reacted with



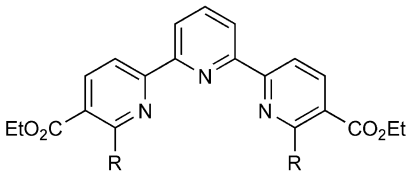
Scheme 1. Synthesis of substituted pyridines.[5]

* Corresponding author. Tel.: +44 191 2274784; fax: +44 191 2273519.
E-mail address: steven.stanforth@unn.ac.uk (S. P. Stanforth).

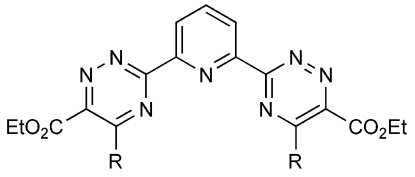
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.128



7



8a R = ^{n}Pr
8b R = Ph



9a R = ^{n}Pr
9b R = Ph

α-acetoxy-α-chloro-β-keto-esters **1** (R^1 = ^{n}Pr or Ph) in the presence of an excess of 2,5-norbornadiene **5** in ethanol at reflux, the 2,2′:6′,2″-terpyridine derivatives **8a** (60%) and **8b** (76%) were obtained following the general sequence outlined above in Scheme 1 without isolation of the corresponding triazine intermediates **9a** and **9b**.[8,9] The structures of the products **8a** and **8b** were fully supported by their spectroscopic data.[8] This method of constructing the 2,2′:6′,2″-terpyridine nucleus is versatile in view of the availability of compounds **1** (from β-keto-esters)[5] and 2,6-dicyanopyridine (commercially available or readily prepared from the inexpensive pyridine-2,6-dicarboxylic acid). Additionally, the reactivity of 1,2,4-triazines towards aza dienophiles other than 2,5-norbornadiene **5** is well known (e.g., enamines)[10] and hence the introduction of additional substituents in the lateral pyridine rings of the 2,2′:6′,2″-terpyridine system should be feasible.

We have therefore demonstrated that our general route to pyridine derivatives depicted in Scheme 1 can be conveniently applied to 2,2′:6′,2″-terpyridine synthesis.

Acknowledgement

We thank Vertellus Specialities Chemicals UK Ltd for generous financial support and the EPSRC mass spectrometry service (Swansea) for high resolution mass spectra.

References and notes

1. Constable, E. C. *Chem. Soc. Rev.* **2007**, *36*, 246–253.
2. Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron Lett.* **2002**, *43*, 6015–6017.
3. Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron Lett.* **2003**, *44*, 693–694.
4. Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron* **2004**, *60*, 8893–8897.
5. Altuna-Urquijo, M.; Stanforth, S. P.; Tarbit, B. *Tetrahedron Lett.* **2005**, *46*, 6111–6113.
6. Gehre, A.; Stanforth, S. P.; Tarbit, B. *Tetrahedron Lett.* **2007**, *48*, 6974–6976.
7. Case, F. H. *J. Heterocycl. Chem.* **1971**, *8*, 1043–1046.
8. *Compound* **8a**: To a solution of compound **1** (R^1 = ^{n}Pr) (501 mg; 2.00 mmol; 2.0 equiv) in EtOH (3 mL) was added $MeNH_2^9$ (0.49 mL; 33% w/w in EtOH; 4.00 mmol; 4.0 equiv) and the mixture was stirred at room temperature for 1 h. The *bis*-amidrazone **7** (193 mg; 1.00 mmol) and 2,5-norbornadiene **5** (2.15 mL; 20.0 mmol; 20.0 equiv) were added and the mixture was heated under reflux for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography [ethyl acetate/petroleum ether (bp 40–60 °C) (1:4)] giving compound **8a** as an off-white solid (279 mg; 60%), mp 105–106 °C (from EtOH). IR (diamond anvil): ν 1721 cm^{-1}. ^{1}H NMR: (270 MHz, $CDCl_3$) δ 8.59 (d, 2H, J = 7.9 Hz), 8.47 (d, 2H, J = 8.3 Hz), 8.30 (d, 2H, J = 8.3 Hz), 7.91 (t, 1H, J = 7.9 Hz), 4.42 (q, 4H, J = 7.2 Hz), 3.26–3.20 (m, 4H), 1.94–1.80 (m, 4 H), 1.44 (t, 6H, J = 7.2 Hz), 1.06 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR: (65 MHz, $CDCl_3$) δ 167.01, 162.79, 157.48, 154.94, 139.42, 137.95, 125.41, 122.31, 117.85, 61.34, 39.05, 23.02, 14.37, 14.30 ppm. HRMS (ES) for $C_{27}H_{32}N_3O_4$ $[M+H]^+$: calcd: 462.2387; measured: 462.2394. Compound **8b** (76%) was prepared using a similar procedure to that described above, mp 156–157 °C (from EtOH). IR (diamond anvil) ν 1704 cm^{-1}. ^{1}H NMR: (270 MHz, $CDCl_3$) δ 8.67 (d, 2H, J = 8.2 Hz), 8.62 (d, 2H, J = 7.9 Hz), 8.27 (d, 2H, J = 8.2 Hz), 7.93 (t, 1H, J = 7.9 Hz), 7.69–7.63 (m, 4H), 7.51–7.43 (m, 6H), 4.19 (q, 4H, J = 7.2 Hz), 1.07 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR: (65 MHz, $CDCl_3$) δ 168.42, 158.35, 157.17, 154.60, 140.49, 139.04, 138.01, 128.92, 128.76, 128.15, 127.13, 122.57, 118.76, 61.57, 13.78 ppm. HRMS (EI) for $C_{33}H_{28}N_3O_4$ $[M+H]^+$: calcd: 530.2074; measured: 530.2079.
9. Methylamine is added to compounds **1** prior to their reactions with amidrazones. We believe that the methylamine reacts at the acetoxy carbonyl group generating compounds **2** by de-acylation followed by chloride elimination. If methylamine is not added, then we have found that 2 equiv of the chloroacetate **1** are required for each $R(NH_2)C{=}NNH_2$ functional group.
10. For a recent example in 2,2′:6′,2″-terpyridine chemistry see: Kozhevnikov, V. N.; Whitwood, A. C.; Bruce, D. W. *Chem. Commun.* **2007**, 3826–3828.