

# Double intramolecular Diels–Alder reaction of $\alpha,\beta$ -unsaturated hydrazones: a new route to 2,2'-bipyridines

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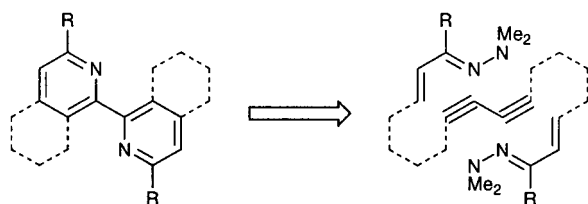
Heating the 1,3-diyne bis- $\alpha,\beta$ -unsaturated hydrazones **3**, **6** and **10** results in double intramolecular Diels–Alder reaction of the 1-azadienes, and after aromatisation by loss of dimethylamine, the formation of bipyridines **11–14**.

In the 110 years since its first preparation, 2,2'-bipyridine has been extensively used as a ligand in organometallic chemistry.<sup>1</sup> Indeed 2,2'-bipyridine is one of the best known, and most effective bidentate ligands for a range of metals, and in recent years chiral bipyridine ligands have found wide use in asymmetric synthesis.<sup>2</sup> We now report a new route to 2,2'-bipyridines based on the double intramolecular Diels–Alder reaction of 1,3-diyne bis- $\alpha,\beta$ -unsaturated hydrazones (Scheme 1).

The preparation of 6-membered ring heterocyclic compounds by the hetero Diels–Alder reaction is now a common tactic in organic synthesis,<sup>3</sup> and the use of azadienes as components in such reactions is established.<sup>4</sup> One useful route to pyridine derivatives is the Diels–Alder reaction of  $\alpha,\beta$ -unsaturated hydrazones with various dienophiles, and since the pioneering work of Ghosez,<sup>5</sup> these 1-azadienes have been used in both inter- and intra-molecular Diels–Alder approaches to pyridine derivatives.<sup>6–8</sup> The intramolecular Diels–Alder (IMDA) reaction of  $\alpha,\beta$ -unsaturated hydrazones with alkynes, first reported in 1988,<sup>8</sup> is a particularly attractive route to annelated pyridines since the initial Diels–Alder adduct readily aromatises by loss of dimethylamine. Therefore we decided to adapt this procedure to the direct synthesis of annelated bipyridines by the simple incorporation of an oxidative homocoupling step giving a 1,3-diyne which would then undergo the desired double IMDA reaction (Scheme 1).

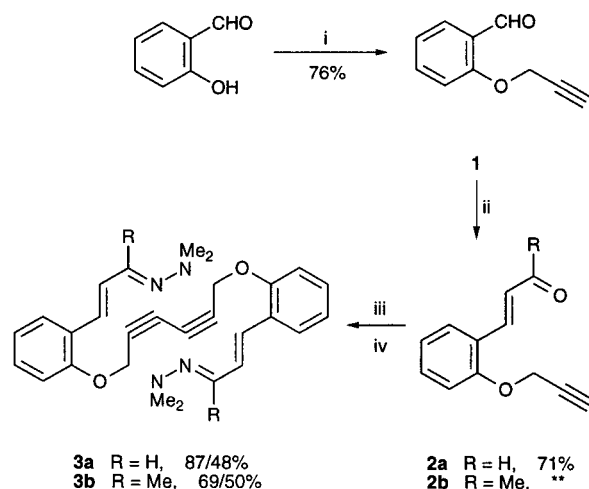
The substrates for the double IMDA reactions were prepared by straightforward routes (Schemes 2–4). The first route involved the alkylation of salicylaldehyde with propargyl chloride (prop-2-ynyl chloride) to give the corresponding aldehyde **1**. Subsequent homologation of the aldehyde with either  $\alpha,\alpha$ -bis(trimethylsilyl)-*N-tert*-butylacetalimine,<sup>9</sup> or with acetylmethylenetriphenylphosphorane gave the  $\alpha,\beta$ -unsaturated aldehydes and ketones **2**. Hydrazone formation followed by Glaser–Eglinton coupling with copper(II) acetate<sup>10</sup> then gave the first substrates **3** for the double IMDA reaction (Scheme 2).

The IMDA substrate **6** was prepared from the known hydrazone **4**<sup>11</sup> by propargylation, and oxidative homocoupling of the alkyne (Scheme 3).

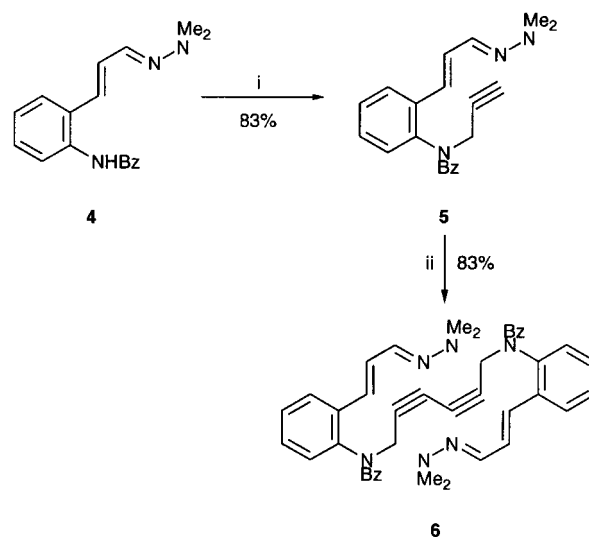


Scheme 1 (Alkynes drawn non-linear for clarity.)

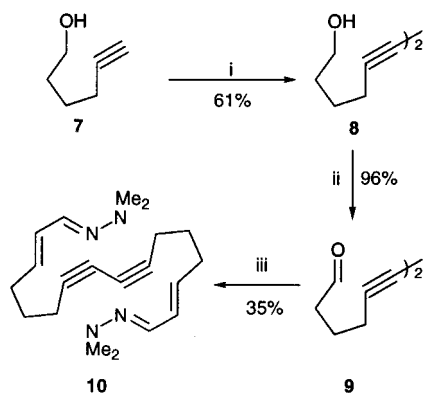
The final substrate investigated was derived from hex-5-ynol **7**, the homocoupling of the terminal acetylene being carried out first (Scheme 4). Thus Glaser–Eglinton coupling of the alkyne gave the corresponding 1,3-diyne **8**; oxidation to the corresponding aldehyde **9** was achieved using *o*-iodylbenzoic acid (IBX) in DMSO.<sup>12</sup> The hydrazone **10** was prepared directly by reaction of **9** with diethoxyphosphonoethanal *N,N*-dimethylhydrazone.<sup>8</sup>



Scheme 2 Reagents and conditions: i,  $\text{HC}\equiv\text{CCH}_2\text{Cl}$ ,  $\text{K}_2\text{CO}_3$ , EtOH; ii, (R = H)  $t\text{-BuN}=\text{CHCH}(\text{TMS})_2$ ,  $\text{ZnBr}_2$ , THF, followed by aq.  $\text{ZnCl}_2$ ; \*\* (R = Me) prepared from salicylaldehyde by reaction with  $\text{Ph}_3\text{P}=\text{CHCOMe}$  (91%), followed by  $\text{HC}\equiv\text{CCH}_2\text{Cl}$ ,  $\text{K}_2\text{CO}_3$ , EtOH (76%); iii,  $\text{Me}_2\text{NNH}_2$ ,  $\text{MgSO}_4$ ,  $\text{CH}_2\text{Cl}_2$ ; iv,  $\text{Cu}(\text{OAc})_2$ , pyridine, MeOH, ether.

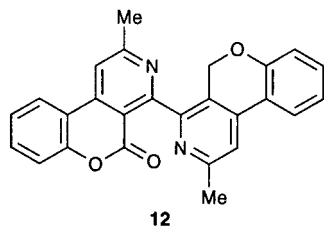


Scheme 3 Reagents and conditions: i,  $\text{HC}\equiv\text{CCH}_2\text{Cl}$ , KH, DMF; ii,  $\text{Cu}(\text{OAc})_2$ , pyridine, MeOH, ether.



**Scheme 4** Reagents and conditions: i,  $\text{Cu}(\text{OAc})_2$ , pyridine, MeOH, ether; ii, IBX, DMSO; iii,  $(\text{EtO})_2\text{POCH}_2\text{CH}=\text{NNMe}_2$ , BuLi, THF.

With a range of substrates in hand, the key double IMDA reactions were carried out. Heating the 1,3-diyne bis-hydrazone **3a** in boiling xylene gave the desired annelated 2,2'-bipyridine as the only isolable product (yield of crude material 60–87%), though considerable losses occurred in purification. The substrate **3b** derived from the  $\alpha,\beta$ -unsaturated ketone was much less satisfactory in the double IMDA reaction; azadiene **3b** gave only 17% of a bipyridine after prolonged heating in mesitylene, though the product was isolated as the mono-oxidation product, the monolactone **12** formed by oxidation at the 5-position of one of



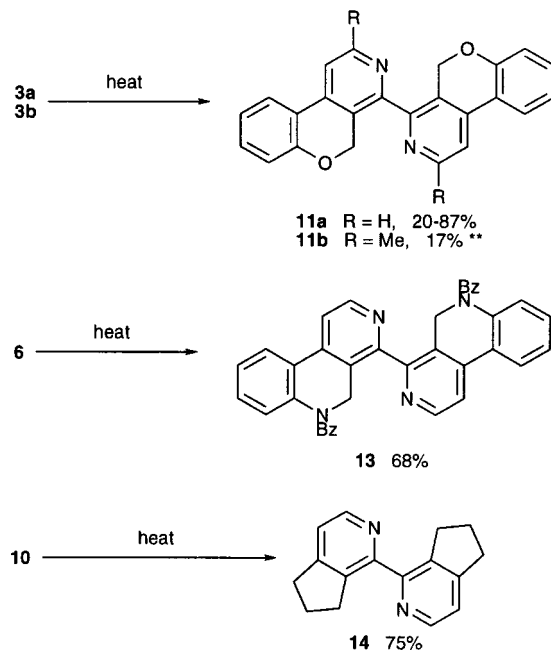
**12**

of the benzopyrano[3,4-*c*]pyridine rings. The *N*-benzoyl compound **6**, a nitrogen analogue of **3a**, underwent smooth double IMDA on heating in xylene to give, after loss of dimethylamine, the 4,4'-bi(benzo[*c*][2,7]naphthyridine) **13** in 68% yield. Finally in the series where the azadiene fragment is connected to the alkyne dienophile by a simple alkyl chain, substrate **10** readily underwent the desired double IMDA reaction in boiling xylene to give the 1,1'-bi(cyclopenta[*c*]pyridine) **14** in good yield (Scheme 5).

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**Scheme 5** (\*\* Isolated as an oxidation product, the monolactone **12** formed by oxidation at the 5-position of one of the benzopyrano[3,4-*c*]pyridine rings.)

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