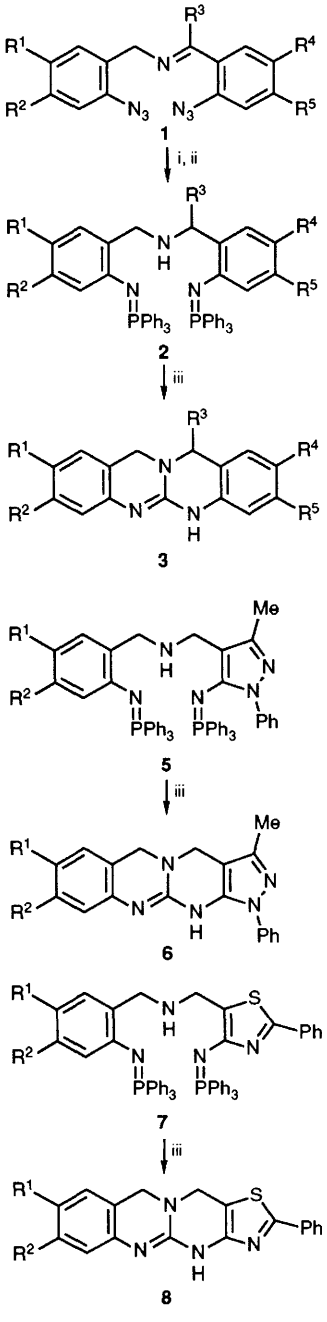
One-pot Preparation of Rigid Bicyclic Guanidines from Bis(iminophosphoranes) by a Consecutive Five-step Process

Pedro Molina,* Mateo Alajarín and Angel Vidal

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Murcia, Campus de Espinardo, E-30071, Murcia, Spain

A one-pot synthesis of bicyclic guanidines based on a new method of dihydropyrimido annelation, which involves reaction of bis(iminophosphoranes) with aromatic isocyanates, is described.

Compounds containing the guanidine moiety are of considerable interest because of a range of biological activities, as versatile very strong organic bases[1] and because they serve as binding sites for anionic functional groups.[2] In this context, rigid bicyclic guanidines have been utilized as enantioselective and/or substrate specific oxoanion hosts.[3] The only method of general value for the preparation of bicyclic guanidines is based on the introduction of the central guanidine carbon atom by a double cyclization process in an open-chain triamine precursor.[4] Continuing our interest on the preparation and synthetic applications of functionalized carbodiimides, we have shown that bis(iminophosphoranes) are valuable building blocks for the preparation of bis(carbodiimides) which undergo a plethora of heterocyclization reactions *via* multistep processes to give complex nitrogen-containing heterocyclic systems.[5] We report herein a one-pot preparation of bicyclic guanidines starting from appropriate bis(azides) **1**. Our synthetic approach, which involves as the key step a consecutive aza Wittig-type reaction–[2 + 2] cycloaddition–transannular dihydropyrimido annelation process has been found to be useful in the simultaneous formation of two dihydropyrimidine rings in the synthesis of bicyclic guanidines.



Scheme 1 *Reagents and conditions*: i, TPP, CH_2Cl_2–diethyl ether, room temp.; ii, $NaBH_4$, MeOH–CH_2Cl_2, 0 °C; iii, 2 equiv. ArNCO, benzene, room temp.

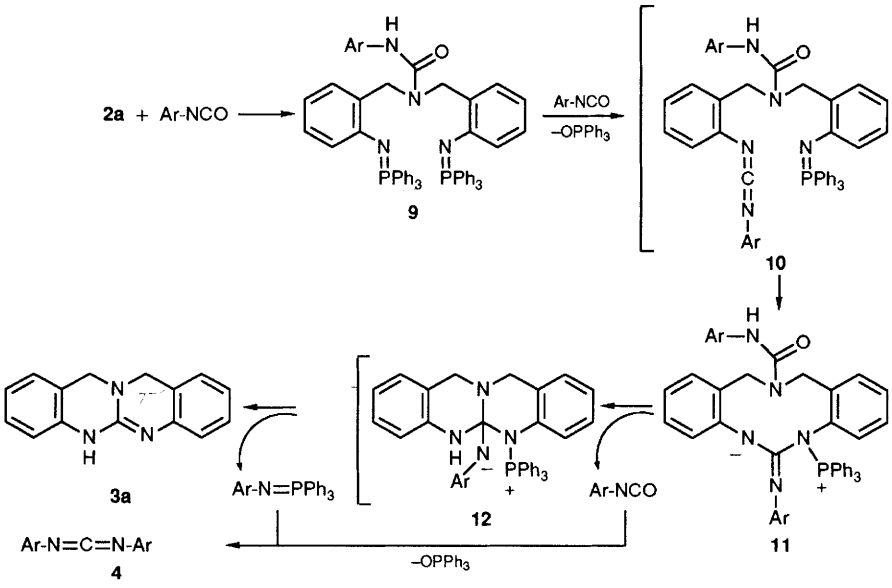
The key intermediates **2** were easily prepared in 60–90% overall yields from bis(azides) **1**, available by condensation of the appropriate *o*-azidobenzaldehydes with *o*-azidobenzylamines, by standard chemistry: Staudinger reaction with triphenylphosphine (TPP) and reduction with sodium borohydride. Bis(iminophosphoranes) **2** were treated with two equivalents of aryl isocyanates, in benzene at room temperature, to produce directly the bicyclic guanidines **3**, which were isolated as crystalline solids in 43–58% yields (Scheme 1, Table 1), the corresponding diarylcarbodiimide **4** and triphenylphosphine oxide. Similar results were achieved when aryl isothiocyanates were used instead of aryl isocyanates.

In an analogous reaction sequence the related bis(iminophosphoranes) **5** and **7** also resulted in the smooth formation of the bicyclic guanidines **6** and **8**. The ^1H and ^{13}C NMR spectra of **6** and **8** exhibited signals very similar to those of compounds **3**. Likewise, other analytical and spectral data confirmed the structure shown.† That conversions of the type **2** → **3**, **5** → **6** and **7** → **8** are reasonably general in nature is indicated by the examples given in Table 1.

Table 1 Bicyclic guanidines **3**, **6** and **8**

Compound	R^1	R^2	R^3	R^4	R^5	Yield(%)
3a	H	H	H	H	H	45
3b	H	H	H	Me	H	43
3c	Me	H	H	Me	H	58
3d	H	H	Me	H	H	57
6a	H	H				45
6b	Me	H				53
6c	H	NO_2				77
8a	H	H				57
8b	Me	H				41

† *Spectroscopic data* for **3c**: ^1H NMR (200 MHz, $CDCl_3$ + CF_3CO_2H) δ 2.31 (s, 6 H), 4.63 (s, 4 H), 6.81 (d, 2 H, *J* 8.2 Hz), 6.91 (s, 2 H), 7.08 (d, 2 H, *J* 8.2 Hz), 9.09 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$ + CF_3CO_2) δ 20.63, 49.83, 115.39 (q), 115.84 (q), 126.39, 128.55 (q), 130.51, 136.28 (q), 146.53 (q); MS *m/z* (%) 263 (M^+, 68), 262 (100); and **8b**: ^1H NMR (200 MHz, $CDCl_3$ + CF_3CO_2H) δ 2.31 (s, 3 H), 4.73 (s, 2 H), 4.91 (s, 2 H), 6.91–6.97 (m, 2 H), 7.13 (d, 1 H, *J* 8.0 Hz), 7.51–7.67 (m, 3 H), 7.78 (d, 2 H, *J* 8.0 Hz), 9.60 (s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$ + CF_3CO_2H) δ 20.57, 47.93, 50.72, 103.68 (q), 115.29 (q), 116.25, 126.41 (q), 127.12, 127.67, 128.48 (q), 130.14, 130.82, 133.68, 137.59 (q), 140.26 (q), 146.37 (q), 172.11 (q); MS *m/z* (%) 332 (M^+, 65), 331 (100).



Scheme 2

Bis(iminophosphoranes) **2** were reacted with one equivalent of aryl isocyanate to give **9** which were recovered unchanged after heating (benzene, reflux, 2 h). However, the reaction of **9** with one equivalent of isocyanate led to the bicyclic guanidines **3**. These observations strongly suggest a mechanism for the conversions **2** → **3**, **5** → **6** and **7** → **8** involving initial addition of one equivalent of the isocyanate on the amino group of **2** to give **9**. An aza Wittig-type reaction between one iminophosphorane group of **9** and the second equivalent of the isocyanate leads to **10**, intramolecular [2 + 2] cycloaddition between the carbodiimide and the iminophosphorane moieties and further P–N bond cleavage affords the intermediate betaine **11**.[6] Molecular models of compound **11** revealed that the amino group of the carbamoyl function and the negative nitrogen atom of the guanidine moiety are very close. As a consequence, elimination from **11** of isocyanate (1 mol), promoted by the negative nitrogen atom of the guanidine portion, with concomitant transannular nucleophilic attack of the nitrogen atom of the amino group on the central carbon atom of the guanidine portion takes place to give **12**, which by loss of *N*-aryl iminophosphorane leads to **3**. Further reaction of the aryl isocyanate with the *N*-aryl iminophosphorane yields the diaryl carbodiimide[7] **4** (Scheme 2).

In conclusion, this work shows for the first time that easily available bis(iminophosphoranes) undergo a one-pot consecutive five-step process to afford bicyclic guanidines.

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