Exploring Cyclopropane-Heterocumulene [3+2] Intramolecular Cycloadditions on ortho-Benzylidene Scaffolds

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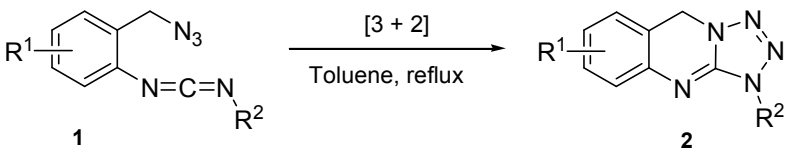
Abstract: We herein report on a new class of intramolecular [3+2] cycloaddition reactions potentially occurring in *N*-aryl heterocumulenes *ortho*-substituted by a cyclopropylidenemethyl unit. The required isothiocyanates, ketenimines and carbodiimides were prepared following aza-Wittig processes of common phosphazene intermediates. To date, only carbodiimides seem to behave as suitable substrates for the desired cyclization.

keywords: [3+2] cycloaddition reactions, heterocumulenes, cyclopropanes, carbodiimides

1.- INTRODUCTION

It is well known that heterocumulene functions of the type X=C=Y are prone to participate in pericyclic processes, mainly in cycloaddition reactions. In a wide variety of such reactions, the heterocumulenic function usually acts as a two-atom component providing one of its two cumulated double bonds.[1]

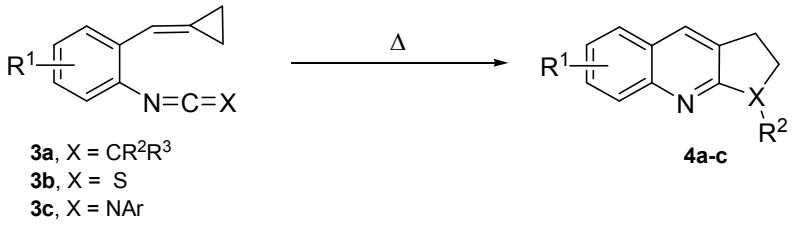
In the course of our recent research on the reactivity of heterocumulenes we have reported that the *ortho*-(azidomethyl)phenyl carbodiimides **1** undergo formal [3+2] intramolecular cycloaddition reactions, by heating in toluene solution at reflux temperature, to give the tetrazolo[5,1-*b*]quinazolines **2**. In these reactions the carbodiimide contributed with the C=N-R^2 double bond to the new five-membered tetrazole ring, whereas the remaining three nitrogen atoms came from the azide function (Scheme 1).[2]



1 **2**

Scheme 1. [3+2] Intramolecular cycloaddition of the *o*-(azidomethyl)phenyl carbodiimide **1**

With this in mind, we reasoned that similar [3+2] cycloadditions could occur in structurally related heterocumulenic compounds **3**, in which the three-atom azido component of species **1** is replaced by a cyclopropane ring, thus forming a new five-membered cyclic unit integrated in the final fused quinolines **4** (Scheme 2).



Scheme 2. Planned [3 + 2] intramolecular cycloadditions of the cyclopropane-heterocumulenes **3**

For an easy access to the starting materials, we planned to link the cyclopropane ring to the *ortho* position of the benzene ring through a methylidene unit, since abundant and simple synthetic methodologies for forming double C=C bonds are available.

2.- EXPERIMENTAL

Preparation of ortho-azidobenzylidenecyclopropane 9

To a stirred suspension of sodium hydride (60% in oil, 6 mmol) in anhydrous tetrahydrofuran (20 mL) cyclopropyltriphenylphosphonium bromide (6 mmol) was added, and the reaction mixture was heated at 60 ºC for 10 h. Next, a solution of 2-azidobenzaldehyde **7** (5 mmol) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) (0.5 mmol) in anhydrous tetrahydrofuran (15 mL) were added and the stirring was continued at the same temperature for 4 h. After that, the reaction mixture was diluted with water (100 mL) and extracted with diethyl ether (3 x 50 mL). The organic layers were combined, washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product so obtained was purified by silica gel column chromatography using hexanes as eluent.

ortho-Azidobenzylidenecyclopropane **9**: yield 59%; oil; IR (Nujol) ν 2120 (vs), 1594 (m), 1575 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15-1.21 (2H, m), 1.37-1.43 (2H, m), 7.00-7.02 (1H, m), 7.08-7.16 (2H, m), 7.24 (1H, td, J = 7.0, 1.6 Hz), 7.78 (1H, dd, J = 7.7, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.7, 4.0, 112.3, 118.3, 124.6, 126.1 (s), 126.8, 127.8, 129.7 (s), 136.4 (s); HRMS (ESI): m/z: calcd for $C_{20}H_{18}N_6$ $[2M + H]^+$: 343.1666; found: 343.1671.

Preparation of the phosphazene 10

To a solution of 1-azido-2-(cyclopropylidenemethyl)benzene **9** (6 mmol) in anhydrous dichloromethane (15 mL) triphenylphosphine (6 mmol) was added. The resulting mixture was stirred at reflux temperature under nitrogen for 4 h. Then, the solvent was removed under reduced pressure and the crude phosphazene was precipitated with diethyl ether and isolated by filtration.

Phosphazene **10**: yield 78%; m.p: 159-160 ºC (colorless prism, from diethyl ether); IR (Nujol) ν 1319 (vs), 1056 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45-1.20 (2H, m), 1.38-1.73 (2H, m), 6.48 (1H, dt, J = 7.8, 1.2 Hz), 6.66 (1H, t, J = 6.6 Hz), 6.76 (1H, td, J = 7.5, 1.8 Hz), 7.41-7.55 (9H, m), 7.75-7.79 (8H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.5, 3.9, 116.1, 117.5, 120.6 (s), 121.8 (d, J = 10.2 Hz), 126.2, 126.8, 128.6 (d, J = 11.8 Hz), 131.6 (d, J = 98.8 Hz) (s), 131.7 (d, J = 2.5 Hz), 132.4 (d, J = 20.7 Hz) (s), 132.7 (d, J = 9.4 Hz), 148.4 (s); ^{31}P NMR ($CDCl_3$, 121.4 MHz, H_3PO_4) δ 1.38; HRMS (ESI): m/z: calcd for $C_{28}H_{24}NP$ $[M + H]^+$: 406.1719; found: 406.1724.

Preparation of 1-(4-methoxyphenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline 4c

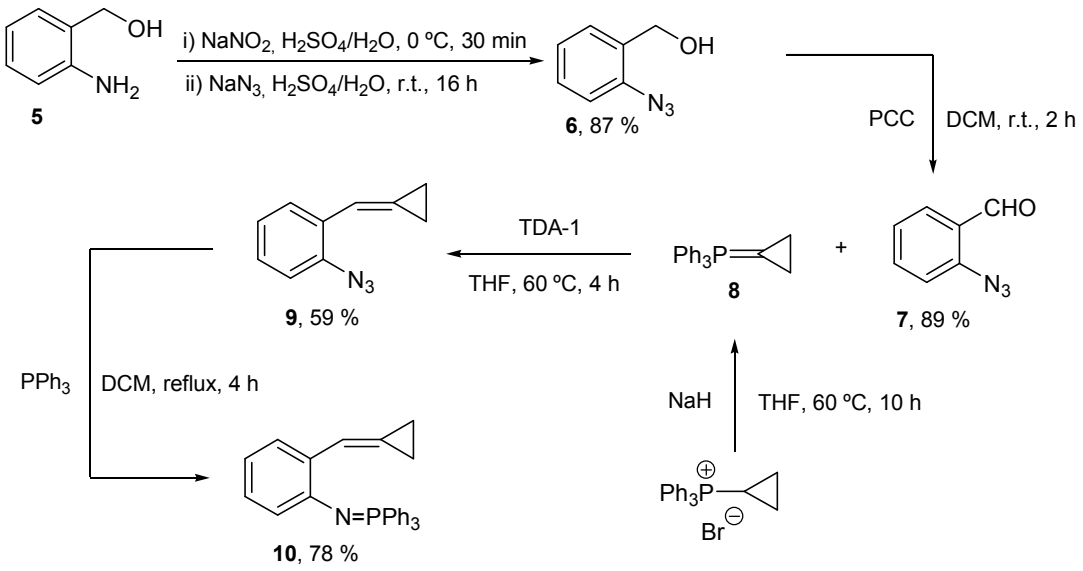
A solution of carbodiimide **4c** (5 mmol) was heated in anhydrous toluene solution at reflux temperature for 3 h. Then, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using hexanes/diethyl ether (3:2, v/v) as eluent.

Pyrrolo[2,3-*b*]quinoline **4c**: Yield 81 %; m.p: 146-148 ºC (colorless prism, from diethyl ether); IR (Nujol) ν 1642 (s), 1571 (m), 1511 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.16 (2H, t, J = 8.1 Hz), 3.83 (3H, s), 4.01 (2H, t, J = 8.1 Hz), 6.98 (2H, d, J = 9.0 Hz), 7.20-7-26 (1H, m), 7.47-7.53 (3H, m), 7.78 (1H, d, J = 8.4 Hz), 7.94 (2H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.6, 48.8, 55.6, 114.1, 119.4, 122.5, 124.3 (s), 126.8, 126.9, 127.0 (s), 128.4, 129.8, 135.5 (s), 147.4 (s), 154.8 (s), 158.6 (s); HRMS (ESI): m/z: calcd for $C_{18}H_{16}N_2O$ $[M + H]^+$: 277.1335; found: 277.1342.

3.- RESULTS AND DISCUSSION

The experimental study started with the selection of the phosphazene **10** as the optimal starting material for opening the access to a variety of heterocumulenic functions, such as ketenimine, carbodiimide and isothiocyanate, via aza-Wittig reactions. The synthetic way to

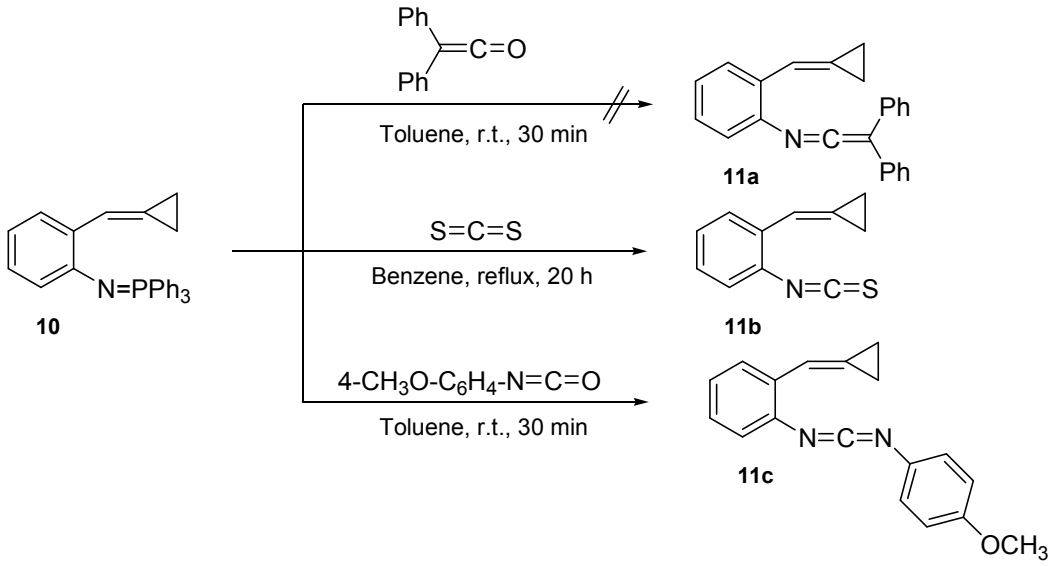
compound **10** started with 2-aminobenzyl alcohol **5**, which was treated with sodium nitrite and aqueous sulphuric acid, cooled at 0 ºC for 30 min, an aqueous sodium azide solution added with stirring at room temperature, and the mixture further stirred for 16 h, yielding 2-azidobenzyl alcohol **6**.[3] In the next step, 2-azidobenzaldehyde **7** was obtained by the oxidation of the benzylic alcohol **6** with pyridinium chlorocromate (PCC) in dichloromethane (DCM) solution at room temperature for 2 h.[4] Next, a Wittig reaction served to install the cyclopropane ring. Thus, cyclopropyltriphenylphosphonium bromide was added to a suspension of sodium hydride in anhydrous tetrahydrofuran (THF), at room temperature, and the mixture was heated at 60 ºC for 10 h, giving rise to a solution of the non-isolated cyclopropylidenephosphorane **8**. After 2-azidobenzaldehyde **7** and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) were added to that THF solution of phosphorane **8**, the resulting reaction mixture was stirred at room temperature for 4 h, yielding *o*-azidobenzylidenecyclopropane **9** in 59% yield. Finally, the Staudinger imination reaction of azide **9** with triphenylphosphine, in anhydrous DCM solution at reflux temperature for 4 h, led to the desired phosphazene **10** in 78% yield (Scheme 3).



Scheme 3. Synthesis of the phosphazene **10**

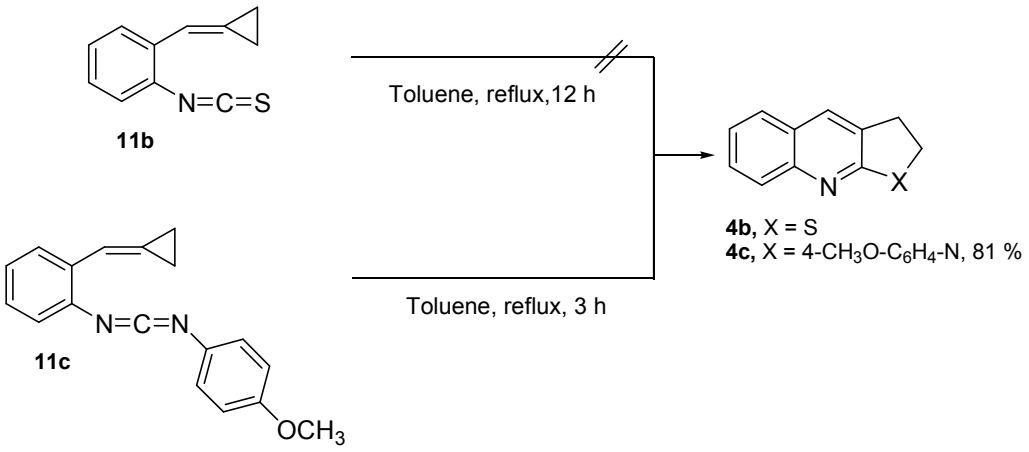
Next we addressed a series of aza-Wittig type reactions of phosphazene **10** with different reagents (diphenylketene, carbon disulfide, 4-methoxyphenylisocyanate) with the aim of obtaining the respective heterocumulenes (ketenimine, isothiocyanate, carbodiimide). For not well-understood reasons, attempts to prepare ketenimine **11a** by reaction of **10** with

diphenylketene under a variety of experimental conditions resulted unsuccessful. In contrast, the preparation of the cyclopropane-bearing isothiocyanate **11b** and carbodiimide **11c** was straightforward. Thus **11b** was prepared by treatment of phosphazene **10** with an excess of carbon disulfide in anhydrous benzene solution at reflux temperature, whereas carbodiimide **11c** was obtained by reaction of phosphazene **10** with 4-methoxyphenylisocyanate in anhydrous toluene solution at room temperature (Scheme 4).



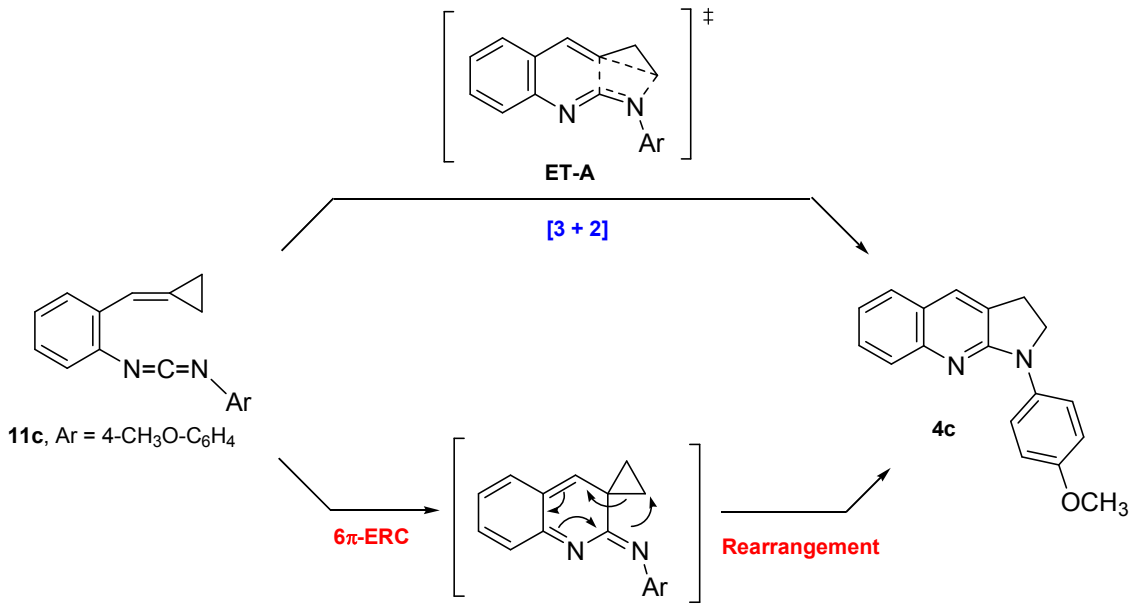
Scheme 4. Synthesis of the cyclopropane-heterocumulenes **11b,c**

Next we tested the planned intramolecular [3+2] cycloaddition reactions of the cyclopropane-heterocumulenes **11** by thermal activation. Unfortunately, when a toluene solution of the isothiocyanate **11b** was heated overnight at reflux temperature, the starting heterocumulene was recovered unaltered, instead of giving rise to the desired thieno[2,3-*b*]quinoline **4b** (X = S). Much to our pleasure, the pyrrolo[2,3-*b*]quinoline **4c** (X = 4-CH_3O-C_6H_4-N) formed in 81 % yield after the carbodiimide **11c** was heated in toluene solution at reflux temperature for 3 h (Scheme 5).



Scheme 5. Thermal treatment of the cyclopropane-heterocumulenes **11b,c**

The conversion of the cyclopropane-carbodiimide **11c** into the pyrrolo[2,3-*b*]quinoline **4c** could be interpreted as the initially planned [3+2] intramolecular cycloaddition, a concerted process *via* the transition state **ET-A**. However a second, two-step mechanistic path is also conceivable for explaining the conversion **11c** → **4c**, involving as a first step the 6π electrocyclic ring closure (6π-ERC) of the carbodiimide **11c** to yield the spiroquinoline intermediate **12**. This electrocyclic process would involve the 2-aza-1,3,5-hexatrienic conjugated fragment formed by one N=C double bond of the carbodiimide group, a C=C double bond of the benzene ring and the C=C double bond of the benzylidene unit.[5,6] Finally, the transient spirocyclic intermediate **12** would undergo an imidoylcyclopropane-pyrrolidine rearrangement, [7] finally leading to the pyrrolo[2,3-*b*]quinoline **4c** (Scheme 6).



Scheme 6. Postulated mechanisms for the conversion of **11c** into the pyrrolo[2,3-*b*]quinoline **4c**

With the aim of shedding light into which of these two reaction paths is the energetically most favourable one for the conversion of **11c** into **4c** we planned to carry out a DFT computational study, which is now underway. We are also currently studying in our laboratories the range of application of the above synthetic methodology for accessing to tricycles **4,** attempting to increase the number of successful transformations of the **11** to **4** type.

4.- CONCLUSIONS

In this communication we have disclosed the successful preparation of two cyclopropane-heterocumulenes (isothiocyanate and carbodiimide) and the results obtained in our attempts of thermally inducing their respective intramolecular [3+2] cycloaddition reactions. Only in the case of the carbodiimide **11c** the expected cycloaddition occurred as planned yielding the corresponding pyrrolo[2,3-*b*]quinoline **4c**. A dichotomy of mechanistic routes to explain that transformation has been proposed, which is now under scrutiny by DFT calculations.

5.- ACKNOWLEDGEMENTS

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6.- REFERENCES

[1] (a) Cossio, F. P.; Arrieta, A.; Lecea, B.; Alajarin, M.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2000**, *65*, 3633. (b) Alajarin, M.; Marin-Luna, M.; Vidal, A. *Eur. J. Org. Chem.* **2012**, 5637.

[2] Alajarin, M.; Bonillo, B.; Ortin, M-M. ; Orenes, R-A.; Vidal, A. *Org. Biomol. Chem.* **2011**, *9*, 6741.

[3] Smolinsky, G. J. *J. Org. Chem.* **1961**, *26*, 4108.

[4] Ardakani, M. A.; Smalley, R. K.; Smith, R. H. *J. Chem. Soc., Perkin. Trans. 1*. **1983**, 2501.

[5] For an example of tandem process 6π-ERC/rearrangement in carbodiimides, see: Li, S.; Luo, Y.; Wu, J. *Org. Lett.* **2011**, *13*, 3190.

[6] For related 6π-electrocyclizations of aryl carbodiimides, see: (a) Saito, T,; Ohmori, H.; Furuno, E.; Motoki, S. *Chem. Commun.* **1992**, 22. (b) Molina, P.; Alajarín, M.; Vidal, A.; Sanchez-Andrada, P. *J. Org. Chem*. **1992**, *57*, 929. (c) Rzepa, H. S.; Molina, P.; Alajarín, M.; Vidal, A. *Tetrahedron*, **1992**, *48*, 7425.

[7] (a) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, 5580. (b) Wasserman, H. H.; Dion, R. P.; Fukuyama, J. *Tetrahedron*, **1989**, *45*, 3203. (c) Kagabu, S.; Ando, C.; Ando, J. *J. Chem. Soc., Perkin. Trans. I* **1994**, 739. (d) Soldevilla, A.; Sampedro, D. *Org. Prep. Proced. Int.* **2007**, *39*, 561.