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).\(^2\)

![Scheme 1. [3+2] Intramolecular cycloaddition of the o-(azidomethyl)phenyl carbodiimide 1](attachment:scheme.png)
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).

\[
\begin{align*}
3a, X &= CR^2R^3 \\
3b, X &= S \\
3c, X &= NAr
\end{align*}
\]

\[R^1 \overset{\Delta}{\longrightarrow} R^2\]

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 °C 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 MgSO₄. 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₀H₁₈N₆ [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 °C (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\(_3\)PO\(_4\)) 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 °C (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\(_2\)O [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 °C 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 °C 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 \( \text{O-azidobenzylidenecyclopropane} \) **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](image)

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$_3$O-C$_6$H$_4$-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. Finally, the transient spirocyclic intermediate 12 would undergo an imidoylcyclopropane-pyrrolidine rearrangement, finally leading to the pyrrolo[2,3-b]quinoline 4c (Scheme 6).
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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