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Intramolecular heteroconjugate addition of heterocumulenes to α,β-unsaturated carbonyl compounds promoted by the CS_2/TBAF system

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Abstract

We describe a new method for the preparation of dihydroquinazoline-2-thione and 4*H*-3,1-benzothiazine-2-thione derivatives by intramolecular heteroconjugate addition of carbodiimides or isothiocyanates bearing one *o*-substituted α,β-unsaturated carbonyl fragment promoted by the CS_2/TBAF system. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Aza-Wittig reaction; azaheterocycles; intramolecular hetero-Michael addition; carbodiimide; isothiocyanate.

The conjugate addition of heteronucleophiles to activated alkenes has often been used in organic synthesis to prepare compounds with heteroatoms β to various activating functional groups.[1] In particular, the aza-Michael addition is noteworthy as a widely used method for the C–N bond formation.[2] Several procedures exist for the intramolecular and intermolecular aza-Michael addition of amides,[3] urea,[4] carbamates,[5] thiolactam[6], guanidines[7] and hydrazine derivatives[8] to electron deficient alkenes. However, the use of heterocumulenes as nitrogen nucleophiles is very rare.

It is known that *N*,*N*′-diarylcarbodiimides bearing one *o*-vinyl substituent undergo a thermally induced 6π-electrocyclization to give quinoline derivatives.[9] In this context, we have reported the first example of an intramolecular heteroconjugate addition of carbodiimides to α,β-unsaturated esters promoted by tetrabutylammonium fluoride (TBAF) to give rise to dihydroquinazolinone derivatives, which represents a formal ureidocyclization process.[10]

We now address the potentiality of this approach to elaborate new dihydroquinazoline derivatives which are of immense importance in the quinazoline series, mainly because their diverse reactions make them convenient intermediates[11] as well as in the pharmaceutical discovery research field. While we were preparing this manuscript, a paper reporting the synthesis

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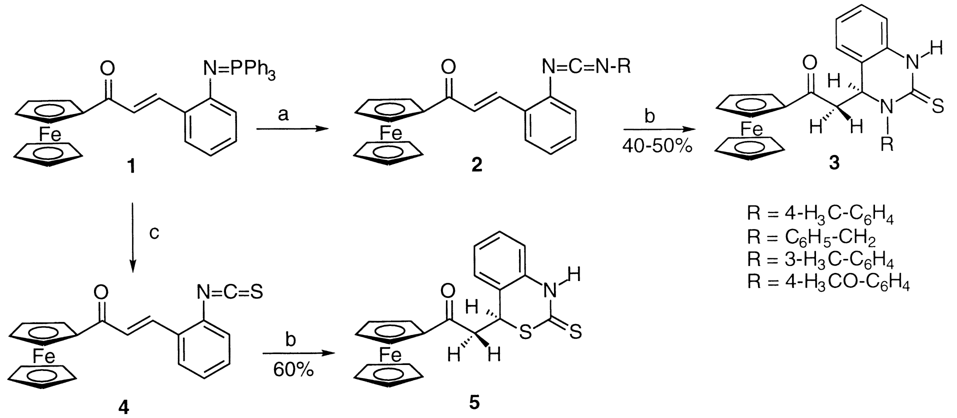
of dihydroquinazoline derivatives via intramolecular hetero-Michael addition of ureas to *o*-substituted α,β-unsaturated esters appeared.[12] This prompts us to report our own results on the TBAF-promoted cyclization of heterocumulenes as a preliminary communication.

In this work we wish to report the peculiar reactivity of carbodiimides **2** and the isothiocyanate **4** toward the CS_2/TBAF system.[13] The aza-Wittig reaction of iminophosphorane **1**[14] with isocyanates in dry dichloromethane gave the corresponding carbodiimides **2**, which were used for the next step without purification. When compounds **2** were treated with the CS_2:TBAF system (4:1 molar ratio) at room temperature for 3 h, the dihydroquinazolinethione derivatives **3** were obtained in yields ranging from 45 to 50%[15] along with a small amount of its oxo-analog.

Iminophosphorane **1** also reacted with CS_2 at 40°C to give the expected isothiocyanate **4**, which by treatment with the CS_2/TBAF system under the same reaction conditions afforded the 4*H*-3,1-benzothiazine-2-thione **5** in 60% yield (Scheme 1). When a 1:1 molar ratio was used, the yields were somewhat lower and the conversion required longer reaction times.

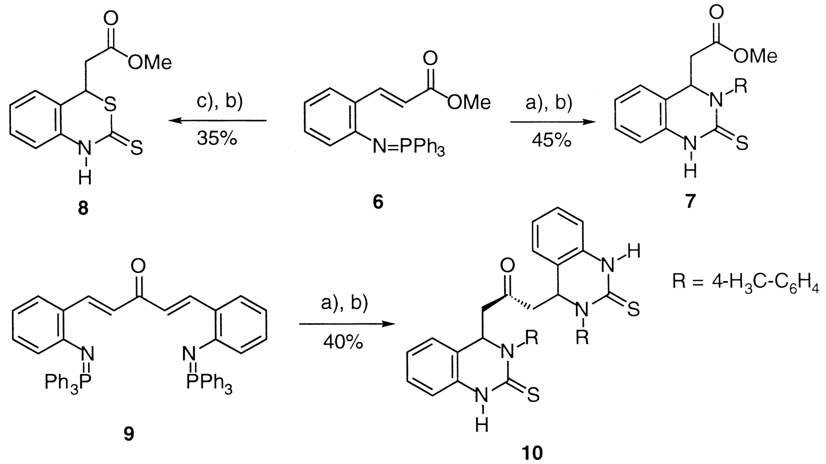


Scheme 1. *Reagents and conditions*: (a) R-NCO, CH_2Cl_2, rt; (b) CS_2/TBAF, rt; (c) CS_2/40°C

In spite of the moderate yields for the conversions **1**→**3** and **1**→**5**, and considering the number of steps: aza-Wittig reaction, activation of heterocumulene moiety and finally cyclization, the yields may be considered as good. The reaction also works with *N*-aryliminophosphoranes bearing an α,β-unsaturated ester moiety in the *ortho* position. Thus, the iminophosphorane **6**[16] was converted into the dihydroquinazoline-2-thione **7** in 45% yield by sequential treatment with *p*-tolylisocyanate and the CS_2:TBAF system (4:1 molar ratio) under the same conditions. Likewise, formation of **8** was achieved in 35% yield by initial conversion into the corresponding isothiocyanate by aza-Wittig reaction with CS_2 followed by TBAF-promoted cyclization[17] (Scheme 2).

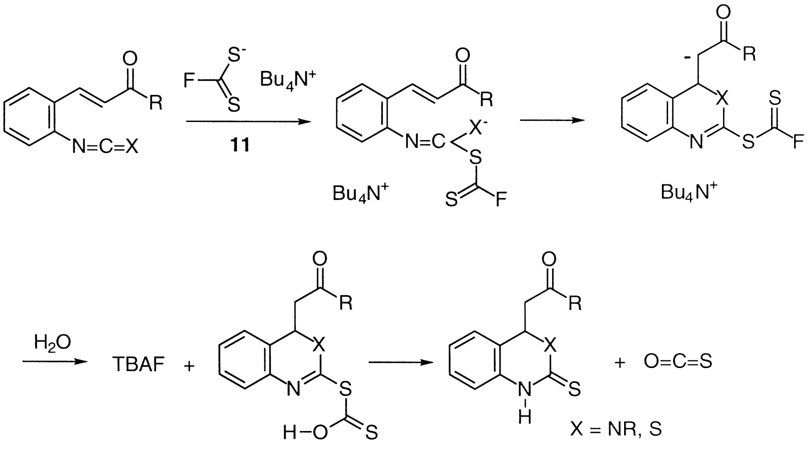
A double annelation process took place when a bis(iminophosphorane) was used as starting material. Bis(iminophosphorane) **9** was prepared in high yield by a two-step sequence: (a) condensation of *o*-azidobenzaldehyde with acetone under basic conditions (58%); and (b) Staudinger reaction of the resulting bis(azide) with triphenylphosphine (70%). Conversion of the bis(iminophosphorane) **9** into the bis(dihydroquinazoline-2-thione) derivative **10** was achieved in 40% yield by using the above-mentioned protocol (Scheme 2).

In these transformations one stereogenic center is formed and the NMR spectra data of compounds **3**, **5**, **7**, **8** and **10** therefore deserve some comment.[18]



Scheme 2. *Reagents and conditions*: (a) R-NCO, CH_2Cl_2, rt; (b) CS_2/TBAF, rt; (c) CS_2/40°C

As far as the mechanism for this kind of cyclization is concerned, we think that the interaction of the TBAF with CS_2 must give rise to a highly reactive S-nucleophile like **11**, with more nucleophilic character than the water present in the reaction medium, which by nucleophilic attack on the central atom of the heterocumulene portion strongly increases the nucleophilic character of the heteroatom (S or N) promoting an intramolecular N- or S-conjugate addition to the *o*-unsaturated side chain in a Michael-type fashion followed by cleavage of the 2-thiosubstituent of the resulting cyclized product either by the water present in the TBAF/THF solution or during the work-up. This mechanism shown in Scheme 3 remains highly speculative. However, we feel it best explains the available experimental results.



Scheme 3.

The work described herein is noteworthy in the following three points. Firstly, the behavior of the carbodiimide moiety as a synthetic equivalent of the thiourea as specific N-nucleophile; this fact is quite important as thiourea is known as a typical ambident nucleophile and generally serves as the S-nucleophile towards electrophile centers. Secondly, the action of the TBAF on the

CS_2 generates a highly reactive S-nucleophile able to react under mild conditions with the central carbon atom of the heterocumulene promoting a new class of thioureido cyclization, being the CS_2 the only source of sulfur. In this context, we have also found that alkyl halides are converted in almost quantitative yield into the corresponding trithiocarbonates by the action of the CS_2/TBAF system. Thirdly, regardless of the mechanistic aspects, this kind of cyclization constitutes a direct access to sulfur-functionalized azaheterocycles, since the described reactions are carried out directly with the starting iminophosphorane without the isolation of the heterocumulene intermediates.

Acknowledgements

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13. The blood red CS_2/TBAF system was prepared by slow addition of the appropriate amount of 1 M TBAF in THF to an excess of CS_2 and vigorous stirring of the resulting mixture for 10 min at room temperature.
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15. *General procedure for the preparation of **3**, **7** and **10***: To a solution of the appropriate iminophosphorane (0.84 mmol) in ahydrous CH_2Cl_2 (15 ml) a solution of an equimolar amount of the adequate isocyanate, in the same solvent (5 ml) was added under nitrogen; the resultant mixture was stirred at room temperature for 8 h and then the preformed CS_2/TBAF system [1 M TBAF/THF (water content 5 wt.%): 3.52 ml and CS_2: 0.85 ml] was added and stirring was continued until the carbodiimide band had completely dissappeared from the IR spectra. The crude was poured into Na_2HPO_4 buffer (pH 7, 20 ml), extracted with CH_2Cl_2 (3×50 ml) and dried ($MgSO_4$). After filtration, the solution was concentrated to dryness and chromatographed on a silica gel column, using ethyl acetate:*n*-hexane (1:1) as eluent to give **3**, **7** and **10**.
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17. *General procedure for the preparation of **5** and **8***: A solution of the corresponding iminophosphorane (0.084 mmol) in CS_2 (30 ml) was heated at 40°C under nitrogen, overnight. When the formation of the isothiocyanate was

complete, the solution was allowed to cool at room temperature and then the preformed CS_2/TBAF system was added. From this step, the work-up followed was the same as that described above.

18. The Fc-CO-CH_2 protons were diastereotopic, appearing in compounds **3** as two double doublets in the region 2.91–3.24 ppm (J = 15.5–17.0 and 10.0–10.6 Hz) and 3.24–3.52 ppm (J = 15.5–17.0 and 3.0–4.0 Hz). Similar chemical shifts and pattern were found for these protons in compound **5** at $\delta = 3.12$ ppm (J = 17.5 and J = 7.5 Hz) and $\delta = 3.40$ ppm (J = 17.5 and J = 7.0 Hz); the methine proton in compounds **3** appeared as a double doublet in the region 5.26–5.50 ppm (J = 10.0–10.6 and 3.0–4.0 Hz), while in compound **5** it appears as a multiplet at $\delta = 4.74$–4.78 ppm. Similarly, the protons of the methylene group in **7** also appeared as two double doublets at $\delta = 2.76$ ppm (J = 15.0 and J = 8.4 Hz) and $\delta = 2.87$ ppm (J = 15.0 and J = 5.1 Hz) and the same pattern was observed for compound **8** at $\delta = 2.80$ (J = 16.5 and J = 6.9 Hz) and $\delta = 2.97$ (J = 16.5 and J = 6.9 Hz). On the other hand, the methine proton in compound **7** appeared as a double doublet at $\delta = 5.22$ (J = 8.4 and J = 5.1 Hz), while in compound **8** appeared as a triplet at $\delta = 4.5$ (J = 6.9 Hz). With reference to compound **10** it is worth noting that two different methyl groups appeared at $\delta = 2.35$ and 2.37 ppm while the protons of the methylene and methine groups appeared as two different multiplets at $\delta = 2.47$–2.91 and 5.12–5.68 ppm, respectively.