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Intramolecular [2 + 2] Cycloaddition of Ketenimines with Imines

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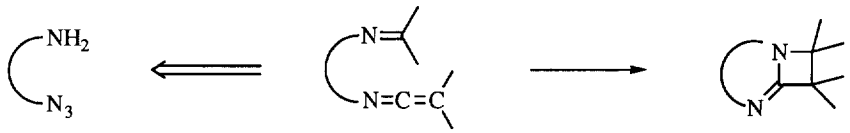
Abstract: *Azeto[2,1-b]quinazolines* ***11*** *have been easily prepared by the novel intramolecular [2 + 2] cycloaddition reaction of ketenimines with imines.* Copyright © 1996 Elsevier Science Ltd

Although ketenimines were first reported by Staudinger in 1921,[1] the development of its chemistry is of relatively recent origin.[2] The chemical behaviour of ketenimines has been explained on the following grounds: i) the electrophilic nature of the α-carbon, which accounts for the addition of a variety of nucleophiles to that *sp*-hybridized carbon atom;[2a] ii) the nucleophilic character of the nitrogen atom, thus allowing reactions with electrophilic species[2c] and the formation of metal σ complexes;[3] iii) the carbon-carbon π bond, being the least sterically shielded, is readily involved in pericyclic processes such as cycloaddition reactions[2] and sigmatropic rearrangements.[4]

[2 + 2] Cycloaddition reactions of keteniminium salts have been well studied[5] and successfully applied in the field of β-lactam synthesis, but similar reactions of ketenimines are scarce.[6] Concerning the *intermolecular* [2 + 2] cycloadditions of ketenimines with imino C=N bonds it has been shown that *N*-alkyl and *N*-aryl ketenimines are poor electrophilic partners and did not react with benzylideneamines PhCH=NR (R = C_6H_5, CH_3).[6a,7] Only the introduction of an electron-withdrawing substituent (tosyl[7] or cyano[8]) on the nitrogen atom of the ketenimine enhanced the electrophilic character of the heterocumulene and allowed the cycloaddition to occur leading to azetidin-2-imines. There are no reports dealing with *intramolecular* versions of such cycloadditions.

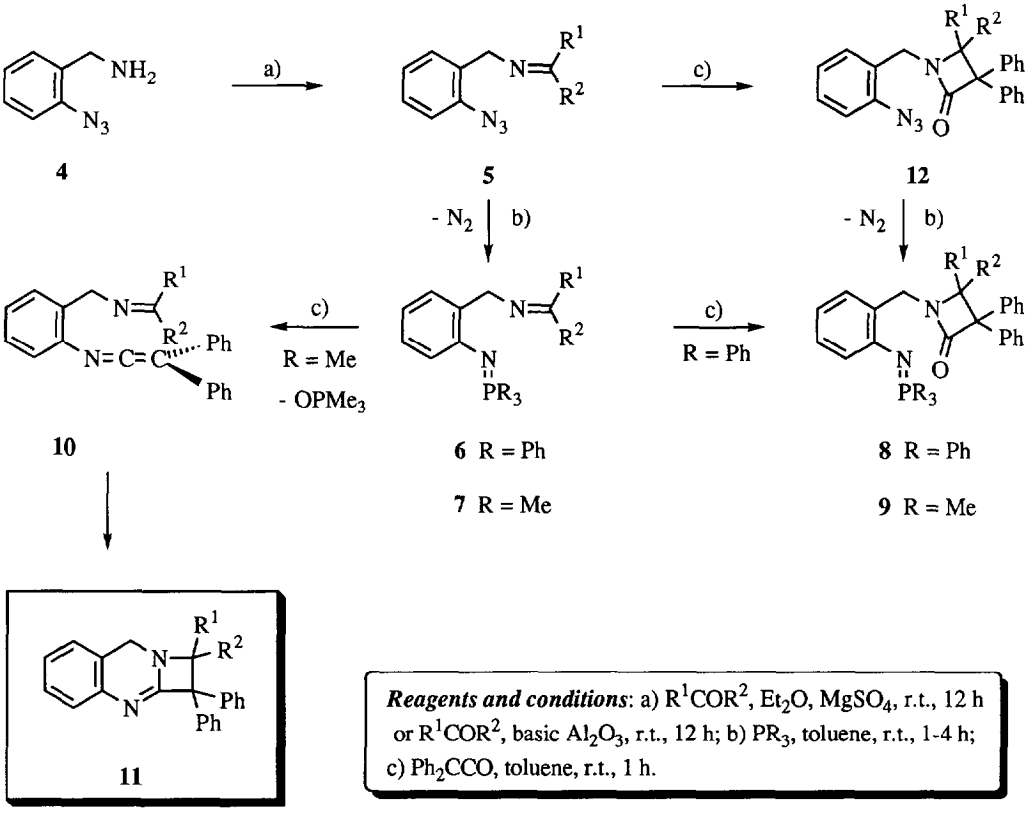
We reasoned that the entropic assistance inherent to intramolecular reactions hopefully would allow to achieve the intramolecular [2 + 2] cycloaddition of ketenimines with imines, in species type **1**, surpassing the constraints imposed to the intermolecular variant by the electronic nature of the substituents, thus opening the way to a variety of fused bicyclic amidines **2** containing an azetidine ring.



3 **1** **2**

Our experience in the chemistry of iminophosphoranes[9] as precursors of ketenimines[4c,e,10] clearly identified the α,ω-azidoamines **3** as the natural building blocks of the required heterocumulenes **1** bearing on its nitrogen atom a *N*-linked imine functionality. Here we describe the first intramolecular [2 + 2] cycloaddition reaction of ketenimines with imines as result of the strategy shown above.

The reaction of 2-azidobenzylamine **4**[11] with aldehydes or ketones under standard conditions[12] led almost quantitatively to the corresponding *N*-(2-azidobenzyl)imines **5** [13,14] which were assumed to be of *E* configuration.[15] Compounds **5** were easily converted into the corresponding triphenyl iminophosphoranes **6** by treatment with triphenylphosphane in toluene solution. To our surprise the C=N bond of compounds **6** proved to be more reactive toward ketenes than the iminophosphorane function: the reaction of **6d** (R^1 = H; R^2 = 4-CH_3O-C_6H_4) with diphenylketene[16] afforded the β-lactam **8d** in 81% yield, instead of the desired ketenimine **10d** which would result from an aza-Wittig type reaction.[17] When the more reactive trimethyl iminophosphoranes **7**, obtained in situ by treatment of **5** with a 1 M toluene solution of trimethylphosphane, were reacted with diphenylketene at room temperature an orange colour quickly developed which slowly faded in less than 1 h to a colourless solution. The IR spectra of the initial reaction mixtures showed strong absorptions around 2000 cm^{-1}, attributable to the C=C=N grouping of the not isolated ketenimines **10**, neatly distinguishable of the one due to diphenylketene (2105 cm^{-1}) which was absent. After chromatographic purification (silica gel column, hexanes/ethyl acetate 4:1 v/v) of the crude products, the previously unknown azeto[2,1-*b*]quinazolines **11** were isolated in moderate to good yields.[18]



Reagents and conditions: a) R^1COR^2, Et_2O, $MgSO_4$, r.t., 12 h or R^1COR^2, basic Al_2O_3, r.t., 12 h; b) PR_3, toluene, r.t., 1-4 h; c) Ph_2CCO, toluene, r.t., 1 h.

In order to additionally prove that compounds **11** resulted from a sequence **7→10→11** and were not formed by an intramolecular aza-Wittig reaction of the iminophosphorane functionalized β-lactams **9** (through a sequence **7→9→11**), the azido β-lactam **12d** (R^1 = H; R^2 = 4-CH_3O-C_6H_4) was prepared by [2 + 2] cycloaddition of **5d** with diphenylketene, and subsequently treated with trimethylphosphane to give **9d** which was stable in toluene solution at room temperature not converting into **11d**.

Table. Azeto[2,1-*b*]quinazolines **11**

Compound	R^1	R^2	(%)[a]
11a	H	$CH(CH_3)_2$	36
11b	H	*E*-CH=CH-C_6H_5	72
11c	H	3-furyl	50
11d	H	4-CH_3O-C_6H_4	63
11e	H	4-O_2N-C_6H_4	81
11f	CH_3	4-O_2N-C_6H_4	46

[a] global yields for the conversion **4→11**

In conclusion, the work described here affords a simple route to several examples of the previously not reported heterocyclic system azeto[2,1-*b*]quinazoline. The key-step of the synthetic sequence, the intramolecular [2 + 2] cycloaddition of ketenimines to imines, is developed here for the first time. Current efforts in our laboratory are directed to the study of the diastereofacial selectivity of such cycloaddition reactions either by using ketenes with enantiotopic faces or by the introduction of stereogenic carbon atoms close to the imine function.

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REFERENCES AND NOTES

1. Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 887.
2. a) Barker M. W.; McHenry, W. E. in *The Chemistry of Ketenes, Allenes, and Related Compounds*, Patai, S., Ed.; Wiley-Interscience: Chichester, England, 1980; Part 2, pp. 701-720; b) Gambaryan, N. P. *Russ. Chem. Rev. (Engl. Transl.)* **1976**, *45*, 630; *Usp. Khim.* **1976**, *45*, 1251; c) Krow, G. R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 435.
3. Aumann, R. *Chem. Ber.* **1993**, *126*, 1867; Merlic, C. A.; Burns, E. E. *Tetrahedron Lett.* **1993**, *34*, 5401 and references cited therein.
4. a) Walters, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11618; b) Walters, M. A.; Hoem, A. B. *J. Org. Chem.* **1994**, *59*, 2645; c) Molina, P.; Alajarín, M.; López-Leonardo, C.; Alcántara, J. *Tetrahedron* **1993**, *49*, 5153; d) Bruckner, R.; Huisgen, R. *Tetrahedron Lett.* **1994**, *35*, 3281; e) Molina, P.; Alajarín, M.;

López-Leonardo, C. *Tetrahedron Lett.* **1991**, *32*, 4041; f) Walters, M. A.; McDonough, C. S.; Brown, P. S., Jr.; Hoem, A. B. *Tetrahedron Lett.* **1991**, *32*, 179.

5. Ghosez, L.; Bogdan, S.; Ceresiat, M.; Frydrych, C.; Marchand-Brynaert, J.; Moya-Portuguez, M.; Huber, I. *Pure Appl. Chem.* **1987**, *59*, 393.
6. For reviews on [2 + 2] cycloaddition reactions of ketenimines see: a) Ghosez, L.; Marchand-Brynaert, J. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I.; Eds. Pergamon Press: Oxford, U. K. 1991; Vol. 5, pp. 108-114; b) Dondoni, A. *Heterocycles* **1980**, *14*, 1567.
7. Van Camp, A.; Gossens, D.; Moya-Portuguez, M.; Marchand-Brynaert, J.; Ghosez, L. *Tetrahedron Lett.* **1980**, *21*, 3081.
8. Arnold, B.; Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 320.
9. Iminophosphoranes are also known as phosphine imines and λ^5-phosphazenes.
10. Molina, P.; Alajarín, M.; Vidal, A.; Foces-Foces, C. *Tetrahedron* **1995**, *51*, 12127; Molina, P.; Alajarín, M.; Vidal, A. *J. Org. Chem.* **1992**, *57*, 6703; Molina, P.; Alajarín, M.; Vidal, A.; Fenau-Dupont, J.; Declerq, J. P. *J. Org. Chem.* **1991**, *56*, 4008; Molina, P.; Alajarín, M.; Vidal, A. *Tetrahedron Lett.* **1991**, *32*, 5379; Molina, P.; Alajarín, M.; Vidal, A.; Fenau-Dupont, J.; Declerq, J. P. *J. Chem. Soc. Chem. Commun.* **1990**, 829.
11. Smith, P. A. S.; Budde, G. F.; Shang-Shing, P. C. *J. Org. Chem.* **1985**, *50*, 2062.
12. Morris, K. G.; Thomas, S. E. *J. Chem.. Soc. Perkin Trans. 1* **1991**, 97; Texier-Boullet, F. *Synthesis* **1985**, 679.
13. Satisfactory ^{1}H-, ^{13}C-NMR, mass spectra and elemental analyses were obtained for all new compounds.
14. Imines **5** were used as crude products in the next step, due to the partial hydrolytic cleavage of the imino bond experienced by some of them during purification attempts by crystallization or column chromatography.
15. ^{1}H- and ^{13}C-NMR data of compounds **5** showed only one set of signals. The chemical shift (16.04 ppm) of the methyl carbon atom in ketimine **5f** (R^1 = CH_3; R^2 = 4-O_2N-C_6H_4) is in accordance with the proposed *E* configuration: Fraser, R. R.; Banville, J.; Akiyama, F.; Chuaqui-Offermanns, N. *Can. J. Chem.* **1981**, *59*, 705.
16. Taylor, E. C.; McKillop, A.; Hawks, G. H. *Org. Synth.* **1973**, *52*, 36.
17. For a recent review see: Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197.
18. **General Procedure:** To a solution of the corresponding *N*-(2-azidobenzyl)imine **5** (3 mmol) in dry toluene (15 mL) trimethylphosphane (3 mmol) was added and the reaction mixture was stirred at room temperature until the evolution of nitrogen ceased (15-30 min). Then diphenylketene (0.58 g, 3 mmol) was added. After stirring at room temperature for 1 h the solvent was removed under reduced pressure and the resulting material was chromatographed on a silica gel column, using hexanes/ethyl acetate (4:1 v/v) as eluent. Compound **11d** (R^1 = H, R^2 = 4-CH_3O-C_6H_4) (63%), m.p. 144-145°C (colourless prisms from Et_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 4.49 (s, 2H), 5.45 (s, 1H), 6.70 (d, 2H, *J* = 8.6 Hz), 6.86 (d, 1H, *J* = 7.2 Hz), 6.97-7.40 (m, 13H), 7.70 (d, 2H, *J* = 8.6 Hz) ; ^{13}CNMR (75 MHz, $CDCl_3$) δ 44.31, 55.16, 70.04 (s), 73.99, 113.62, 121.21(s), 124.40, 125.69, 126.57, 127.02, 127.15, 127.69, 127.76, 128.35, 128.50, 128.54, 128.95, 137.96 (s), 141.67 (s), 143.24 (s), 159.53 (s), 165.25 (s), one quaternary carbon was not observed ; IR (Nujol) 1668, 1598, 1512, 1246,1173, 1025 cm^{-1}; EI mass spectrum m/z (%) 416 (M^+, 76), 165 (100).

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