The First Aza-Wittig Reaction of the β-Lactam Carbonyl Group

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Received 24 July 1998

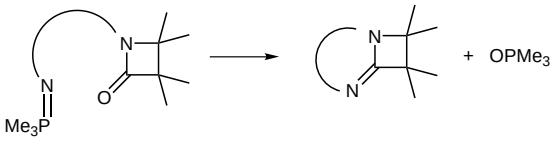
Abstract: The imination of the β-lactam carbonyl group by the aza-Wittig reaction is described. The process is only amenable when carried out intramolecularly.

The reaction of λ^5-phosphazenes (iminophosphoranes, phosphine imines) with carbonyl compounds affording the corresponding imination products is known as the aza-Wittig reaction, and its synthetic relevance has been summarized in several review articles.[1] The intramolecular version of this reaction has drawn considerable attention because of its high potential in heterocyclic synthesis.[1b,e]

The reactivity towards cyclization of the intramolecular aza-Wittig reaction is controlled by several factors: chain length (product ring size and ring strain), the substituents at the P and N atoms of the phosphazene function, and the chemical nature of the carbonyl group. Concerning the last one, whereas participation of imide carbonyl groups in such reactions is now well established,[2] only a few examples of intramolecular aza-Wittig reactions involving less reactive amide carbonyl groups are known,[3] usually suffering of low yields.

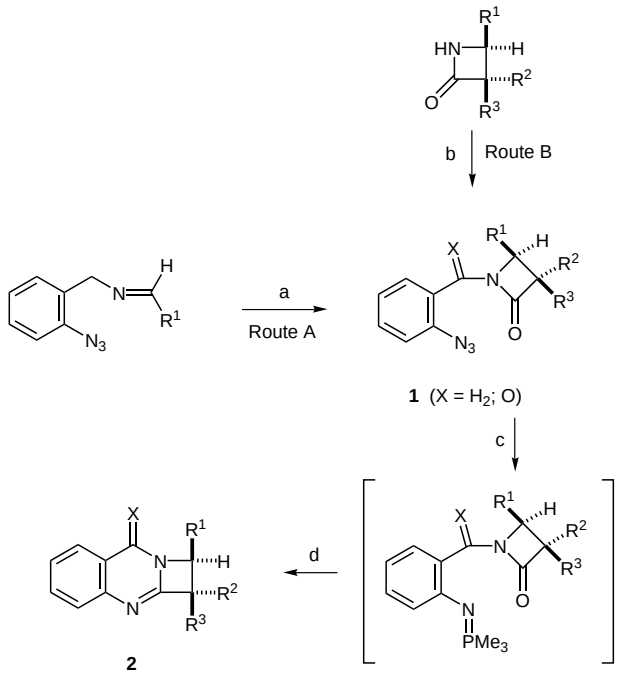
To our knowledge there are no reported examples of successful aza-Wittig reactions involving the carbonyl group of a β-lactam ring. Moreover, two literature reports[4] dealing with *inter*molecular attempts to carry out such process were disappointing.

Herein we report that the imination of a β-lactam carbonyl group by the aza-Wittig reaction is synthetically amenable when carried out *intra*molecularly, provided that reactive *P,P,P*-trimethyl-λ^5-phosphazenes are used as the imination reagents.



In the course of our research on the intramolecular [2 + 2] cycloaddition of ketenimines with imines,[5] an easy access to *N*-(2-azidobenzyl)-β-lactams **1** (X = H_2; $R^2 = R^3 = C_6H_5$) was accomplished by the reaction of *N*-(2-azidobenzyl) aldimines with diphenylketene.[5a] In that way, azido-β-lactams **1a-c** have been prepared (Route A, Scheme 1). For the preparation of compounds **1d-l** the more convenient *N*-alkylation[6] or acylation[7] of commercially available or easily synthesized *N*-unsubstituted β-lactams with 2-azidobenzyl iodide[8] or 2-azidobenzoyl chloride[9] respectively, was the method of choice (Route B).[10]

Initial attempts to achieve the conversion of compounds **1** to the corresponding azeto[2,1-*b*]quinazolines **2** (X = H_2) or quinazolin-8-ones **2** (X = O) by treatment with PPh_3 or PBu_3 under different reaction conditions (solvent, temperature) were unsuccessful, leading to complex mixtures in which the desired products could not be detected by tlc.[11] More satisfactorily, when a 1 M toluene solution of PMe_3 was used to effect the conversion of the azido group in **1** to the non-isolated *N*-aryl-*P,P,P*-trimethyl-λ^5-phosphazene (nitrogen evolution was clearly observed) and the resulting toluene solution was refluxed under nitrogen for 12-24 h, the corresponding benzo-fused bicyclic amidines **2** were obtained in variable yields (40-90%) (Scheme 1, Table).[12]



Reagents and conditions: (a) $R^2R^3C{=}C{=}O$, toluene, r.t., 1h; (b) 2-N_3-C_6H_4-CH_2I , K_2CO_3, cat. *n*-Bu_4NBr, acetonitrile, reflux, 20 h or 2-N_3-C_6H_4-COCl, Et_3N, CH_2Cl_2, 0°C, 1 h, then r.t., 12 h; (c) PMe_3, toluene, r.t., 10 min; (d) toluene, reflux, 12-24 h.

Scheme 1

Due to the extreme hydrolytic susceptibility of the trimethylphosphazene group, strict anhydrous conditions were required for the success of these reactions. In some cases the chromatographic purification of the reaction products caused the oxidation of azeto[2,1-*b*]quinazolines **2** (X = H_2) to quinazolin-8-ones **2** (X = O), which occasionally render difficult the isolation of pure **2** (X = H_2). This spontaneous oxidation is not unprecedented[5b] and was particularly notable in product **2e**, where flash column chromatography and exclusion of sunlight were unable to suppress this phenomenon.

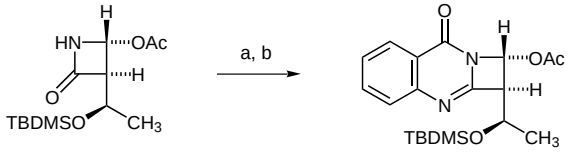
Table. Azeto[2,1-*b*]quinazolines and azeto[2,1-*b*]quinazolin-8-ones **2**.

Label	X	R^1	R^2	R^3	(%)[a]
a	H_2	4-Cl-C_6H_4	C_6H_5	C_6H_5	47
b	H_2	4-CH_3-C_6H_4	C_6H_5	C_6H_5	44
c	H_2	4-O_2N-C_6H_4	C_6H_5	C_6H_5	84
d	H_2	H	H	H	67[b]
e	H_2	C_6H_5	H	H	60
f	H_2	4-CH_3-C_6H_4	CH_3	H	41
g	H_2	4-CH_3O-C_6H_4	CH_3	H	40
h	O	H	H	H	90
i	O	C_6H_5	H	H	88
j	O	CH_3COO	H	H	50
k	O	C_6H_5COO	H	H	65
l	O	4-CH_3-C_6H_4	CH_3	H	70

[a] Yield for the conversion **1**→**2**. [b] Isolated as its oxidation product **2h**.

Spectroscopic identification of compounds **2** was accomplished by the usual techniques (IR, ^{1}H and ^{13}C NMR, MS).[13] The course of the conversion **1** → **2** could be monitored by the decreasing intensity of the IR absorption due to the carbonyl group of **1** at 1760-1810 cm^{-1} and the subsequent increasing of the C=N band of **2** at 1660-1680 cm^{-1}. Detection of O=PMe$_3$[14] in the final reaction mixtures corroborated the aza-Wittig nature of these reactions.

The examples reported so far involved achiral or racemic azido-β-lactams **1**. The present method was also applicable to the preparation of azeto[2,1-*b*]quinazolin-8-one **4** in 47% yield,[15] starting from the commercially available, enantioenriched β-lactam **3** (Scheme 2).

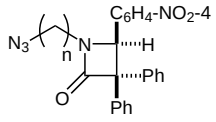


3 **4**

Reagents and conditions: (a) 2-N$_3$-C$_6$H$_4$-COCl, Et$_3$N, CH$_2$Cl$_2$, 0°C, 1 h, then r.t., 12 h; (b) PMe$_3$, toluene, r.t., 10 min, then reflux, 12 h.

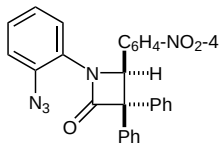
Scheme 2

Attempts to carry out reactions similar to the ones summarized in the Table but *inter*molecularly, by the employment of several *N*-substituted (alkyl, acyl) β-lactams and the phosphazenes PhCH$_2$N=PMe$_3$ and PhCON=PMe$_3$ (generated in situ from the azides and PMe$_3$), failed. Other *intra*molecular attempts, starting from alkyl azides **5** and **6**, or aryl azide **7**, also resulted in failure.



5 n = 2

6 n = 3



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These last results were relevant in order to quote the scope and applicability of the method: reactions involving aliphatic azide fragments or leading to five-membered rings did not work properly.

In conclusion, the aza-Wittig imination of β-lactam carbonyl groups by the action of λ^5-phosphazenes has been achieved, for the first time, in an *intra*molecular manner to yield azeto[2,1-*b*]quinazolines or quinazolin-8-ones. The method requires the intermediacy of highly reactive *N*-aryl-*P,P,P*-trimethyl-λ^5-phospha-zenes, and it has only proven useful when it results in the formation of a six-membered ring.

Acknowledgements: The authors wish to thank the Dirección General de Investigación Científica y Técnica (DGICYT) for financial support (project number PB95-1019). One of us (F.T.) also thanks the MEC for a fellowship.

References and notes

(1) a) Wamhoff, H.; Rechardt, G.; Stölben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 159; b) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197; c) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209; d) Barluenga J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1; e) Gusar, N. I. *Russ. Chem. Rev. (Engl. Transl.)* **1991**, *60*, 146.

(3) Kurita, J.; Iwata, T.; Yasuike, S.; Tsuchiya, T. *J. Chem. Soc., Chem. Commun.* **1992**, 81; Molina, P.; Alajarín, M.; López-Leonardo, C.; Madrid, I.; Foces-Foces, C.; Cano, F. H. *Tetrahedron* **1989**, *45*, 1823; Molina, P.; Alajarín, M.; Vidal, A.; Elguero, J.; Claramunt, R. M. *Tetrahedron* **1988**, *44*, 2249; Gololobov, Y. G.; Gusar, N. I.; Chaus, M. P. *Tetrahedron* **1985**, *41*, 793; Flitsch, W.; Mukidjam, E. *Chem. Ber.* **1979**, *112*, 3577.

(4) L'abbé, G.; Sorgeloos, D.; Toppet, S. *Tetrahedron Lett.* **1982**, *23*, 2909; Marchand-Brynaert, J.; Ghosez, L. In *Recent Progress in the Chemical Synthesis of Antibiotics*, Lukacs, G. and Ohno, M., Eds.; Springer-Verlag: Berlin, 1990, p 733.

(5) a) Alajarín, M.; Molina, P.; Vidal, A. *Tetrahedron Lett.* **1996**, *37*, 8945; b) Alajarín, M.; Molina, P.; Vidal, A.; Tovar, F. *Tetrahedron* **1997**, *53*, 13449.

(6) Chmielewski, M.; Kaluza, Z.; Abramski, W.; Belzecki, C. *Tetrahedron Lett.* **1987**, *28*, 3035.

(7) See for instance: Sakurai, O.; Ogiku, T.; Takahashi, M.; Hayashi, M.; Yamanaka, T.; Horikawa, H.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 7889.

(8) Alajarín, M.; López-Lázaro, A.; Vidal, A.; Berná, J. *Chem. Eur. J.*, in press.

(9) Porter, T. C.; Smalley, R. K.; Teguiche, M.; Purwono, B. *Synthesis* **1997**, 773.

Typical Experimental Procedure for the Alkylation of *N*-Unsubstituted β-Lactams. Tetrabutylammonium bromide (0.26 g, 0.8 mmol) and K_2CO_3 (4.42 g, 32 mmol) were added to a solution of 2-azidobenzyl iodide (1.24 g, 4 mmol) and the corresponding 2-azetidinone (4 mmol) in dry acetonitrile (40 ml). The mixture was stirred at reflux temperature for 24 h. After cooling the mixture was poured into water (100 ml) and extracted with CH_2Cl_2 (3 x 40 ml). The combined organic layer was washed with water (100 ml) and brine (100 ml), dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (silica gel; elution with *n*-hexane: EtOAc).

Data for **1e**: mp 148°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (dd, *J* = 2.4, 14.7 Hz, 1H), 3.36 (dd, *J* = 5.1, 14.7 Hz, 1H), 3.96 (d, *J* = 14.9 Hz, 1H), 4.42 (dd, *J* = 2.4, 5.1 Hz, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 7.03-7.09 (m, 2H), 7.17-7.37 (m, 7H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 40.37, 47.05, 54.46, 118.16, 124.98, 126.45, 126.74, 128.45, 128.86, 129.37, 131.03, 128.28, 138.44, 167.34; IR (Nujol) 2122, 1754, 1406, 1305, 755, 701 cm^{-1}; MS (EI) m/z (%) 278 (M$^+$, 24), 103 (100); Anal. Calcd. for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.83; H, 5.21; N, 20.01.

Typical Experimental Procedure for the Acylation of *N*-Unsubstituted β-Lactams. To a solution of the corresponding 2-azetidinone (3 mmol) and 2-azidobenzoyl chloride (1.63 g, 9 mmol) in dry CH_2Cl_2 (30 ml), with ice cooling, was added dropwise a solution of Et_3N (3.03 g, 30 mmol) in dry CH_2Cl_2 (15 ml), and the mixture was stirred overnight. Then the mixture was poured into water (100 ml), and extracted with CH_2Cl_2 (2 x 25 ml). The combined organic layer was washed with saturated $NaHCO_3$ aqueous solution (2 x 100 ml), water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, elution with *n*-hexane/ EtOAc).

Data for **1i**: mp 130°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02 (dd, *J* = 3.7, 16.5 Hz, 1H), 3.53 (dd, *J* = 6.5, 16.5 Hz, 1H), 5.22 (dd, *J* = 3.7, 6.5 Hz, 1H), 7.18-7.26 (m, 2H), 7.32-7.56 (m, 7H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 45.81, 52.98, 118.68, 124.67, 125.95,

126.07, 128.43, 128.92, 129.82, 132.63, 137.81, 138.68, 163.21, 163.76; IR (Nujol) 2134, 1811, 1679 cm^{-1}; MS (EI) m/z (%) 292 (M^+, 11), 104 (100); Anal. Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.87; H, 4.03; N, 19.34.

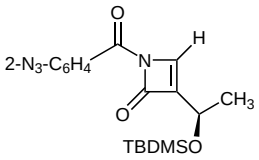
(11) Compound **2c** has been previously prepared by us through a different methodology, see ref. 5b.

(12) **Typical Experimental Procedure for the Preparation of Azeto[2,1-*b*]quinazolines and Azeto[2,1-b]quinazolin-8-ones 2**. To a solution of the 2-azetidinone **1** (1 mmol) in dry toluene (15 ml) trimethylphosphane was added (1.0 ml of a 1 M toluene solution), and the mixture was stirred at room temperature until the evolution of nitrogen ceased (5-10 min). Then the solution was heated at reflux temperature for 12-24 h. After cooling, the solvent was removed under reduced pressure and the resulting material was chromatographed (silica gel; elution with *n*-hexane/EtOAc).

(13) Data for **2j**: mp 125°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.51 (dd, *J* = 1.9, 16.2 Hz, 1H), 3.93 (dd, *J* = 4.3, 16.2 Hz, 1H), 6.90 (dd, *J* = 1.9, 4.3 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.59, 41.72, 78.59, 123.32, 126.55, 126.84, 127.24, 134.34, 149.87, 154.57, 157.33, 168.93; IR (Nujol) 1759, 1684, 1659, 1221, 775 cm^{-1}; MS (EI) m/z (%) 230 (M^+, 34), 43 (100); Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.74; H, 4.23; N, 12.23.

(14) O=PMe_3: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.52 (d, $^2J_{HP}$ 12.9 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$, 85% H_3PO_4) δ 36.0.

(15) Compound **4** thus obtained was impurified by a minor amount (approximately 20%, as revealed by ^{1}H NMR analysis) of a second diastereoisomer. The mixture could not be chromatographically resolved into its two components. The *trans* configuration of both diastereoisomers was unambiguously deduced from the values of the coupling constant between the protons at the sp^3 carbon atoms of the azetidine ring: 1.7 and 1.3 Hz for the major and minor diastereoisomer respectively. The same ratio of diastereoisomers (4:1) was also present in the acylation product resulting from the first step of the sequence depicted in Scheme 2. It is reasonable to assume, albeit speculatively, the (1*R*,2*R*,1'*R*) and (1*S*,2*S*,1'*R*) configurations for the major and minor diastereoisomers of **4**, the minor one arising from partial racemization at the sp^3 carbon atoms of the β-lactam ring during the base-catalysed *N*-acylation step, probably through the intermediacy of the azetone *A*.



A

It is well known that 4-acyloxy-β-lactams are configurationally unstable under basic conditions (Kametani, T.; Honda, T.; Nakayama, A.; Sasaki, Y.; Mochizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2228 and references therein).