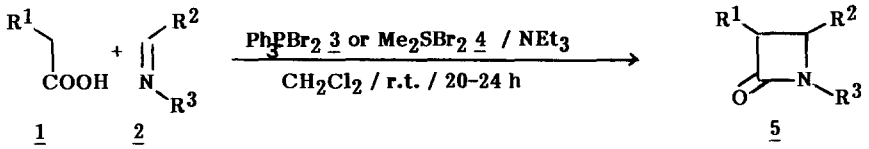
Tetrahedron Letters,Vol.26,No.25,pp 3041-3044,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

TRIPHENYLPHOSPHINE DIBROMIDE AND DIMETHYLSULFIDE DIBROMIDE AS VERSATILE REAGENTS FOR BETA-LACTAM SYNTHESIS [1]

Fernando P. Cossío, Iñaki Ganboa and Claudio Palomo*
Kimika Organikako Departamendua, Kimika Fakultatea Euskal Herriko
Unibertsitatea. Altza. Donostia. Spain.

Summary : Triphenylphosphine dibromide and dimethylsulfide dibromide are efficient reagents for the direct synthesis of beta-lactams from carboxylic acids and imines avoiding the use of acid halides as starting materials. Synthesis of 4-imino-beta-lactams are also briefly described. A potential synthesis of N-unsubstituted beta-lactams is made.

Since the discovery of non classical beta-lactam antibiotics the development of synthetic methods for the synthesis of 3-substituted-beta-lactams has been the object of intense study by a number of research groups. A widely used method for the synthesis of variously substituted beta-lactams is the reaction between an imino compound and an acid chloride in presence of a tertiary base. However, this method is not convenient when the acid chloride is not available or not always simple to prepare. This communication reports that triphenylphosphine dibromide 3 , a widely used reagent in organic synthesis [2], is an excellent reagent for the synthesis of 3-substituted beta-lactams 5 from acetic acids 1 and imines 2 , under mild reaction conditions. To our knowledge no reports have been described concerning to the use of this reagent in beta-lactam synthesis [3].



1 2 5

Preparation of reagents

Triphenylphosphine dibromide 3 was prepared as follows : bromine (1 ml, 20 mmol) in dry dichloromethane (10 ml) was added dropwisse to a stirred solution of triphenylphosphine (5.4 g, 20 mmol) in the same solvent (15 ml) at 0ºC. The obtained suspension of the reagent 3 was used as such. Dimethylsulfide dibromide 4 was prepared in a similar manner, thus, bromine (20 mmol) in dry dichloromethane (10 ml) was added dropwisse to a stirred solution of dimethylsulfide (1.46 ml, 20 mmol) in dichloromethane (20 ml) at 0ºC and the obtained suspension of the reagent 4 was used as such.

Preparation of beta-lactams

A general procedure is given as follows : To the suspension of triphenylphosphine dibromide (20 mmol) , an acetic acid (20 mmol), triethylamine (7 ml , 50 mmol) and an imine (15 mmol) were consecutively added at

Table I. Beta-lactams 5 prepared from reagent 3

5	R^1	R^2	R^3	Conf.[c]	Yield[d] (%)	m.p.ºC found	m.p.ºC lit.
a	Cl_2 [a]	C_6H_5	C_6H_5	———	50(15)	163-164	164[10]
b	Pht [b]	C_6H_5	C_6H_5	trans	50(20)	229-230.5	230-231[11]
c	Pht [b]	4-$CH_3OC_6H_4$	C_6H_5	trans	65	236-237	236-237[11]
d	C_6H_5O	C_6H_5	C_6H_5	cis	55(25)	190-192	192-194[4]
e	4-$CH_3OC_6H_4$	C_6H_5	C_6H_5	trans	46	200-204	200-204[4]
f	CH_3O	C_6H_5	C_6H_5	cis	40	138-140	141-142[4]
g	C_6H_5O	4-$CH_3OC_6H_4$	CH_2CH_2OH	cis	50	146-148	———
h	C_6H_5O	4-$CH_3OC_6H_4$	$CH_2CH(OH)Ph$	cis	55	175-177	———

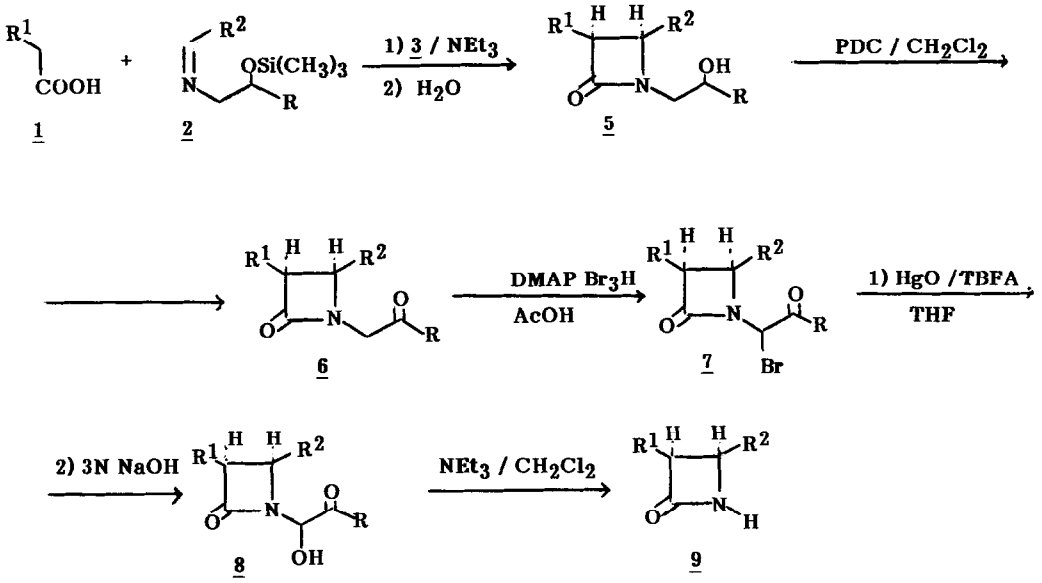
a) Cl_2 : 3-dichloro; b) Pht: Phthalimido group; c) configuration of C-3 and C-4 protons was determined by pmr spectroscopy; d) yield of isolated pure product; recrystallization from ethanol-hexane; yield in parenthesis refered to beta-lactams 5 prepared from reagent 4.

0ºC. The resulting mixture was stirred at room temperature for 20-24 h and then washed with water. The organic layer was dried with sodium sulfate and evaporation of the solvent gives a solid residue which was triturated with ethanol to give the beta-lactam 5 which was recrystallized from ethanol-hexane. All products were identified by physical and spectroscopic characteristics. Under similar conditions some beta-lactams were prepared from reagent 4 . From the examples listed in table I, the reagent 3 displays general scope, since various carboxylic acids and imines are readily cyclisized to their corresponding beta-lactams in yields being in the range 40% to 60%. It is noteworthy that for compounds 5d and 5f the acid chloride method[4] lead to the formation of mixtures of cis- and trans-beta-lactams, however by our procedure a single isomer was obtained for such beta-lactams[5]. A key feature of these beta-lactams is shown by their use as potential precursors of N-unsubstituted beta-lactams; thus, pyridinium dichromate (PDC) oxidation of 5h gives beta-lactam 6h (30 h, 60% yield, m.p. 99-102ºC); ^{1}H NMR ($CDCl_3$) δ ppm : 7.7-6.1 (m,14H,arom.), 5.4 (d,J = 5 Hz, 1H,CH), 5.1(d,J = 5 Hz,1H,CH), 4.9 (d,J = - 18 Hz, 1H,NCHCO), 3.9(d,J = - 18 Hz,1H,NCHCO), 3.5(s,3H,OCH_3). Treatment of 6h with 4-dimethylaminopyridinium bromide perbromide[6a] (DMAP HBr_3) affords the corresponding α-bromo ketone 7h (15 min, 86% yield, m.p. 110-112ºC)[6b] . This α-bromo compound was converted into the amidocarbinol 8h following Barluenga's procedure[7a] , which was " in situ" treated with equimolar amounts of triethylamine for a few hours to give the N-unsubstituted beta-lactam 9 in 35% yield, m.p. 167-169ºC (lit. 166-167ºC)[7b] (Scheme I).

Preparation of imino beta-lactams

A further utility of our method is that reaction of acetic acids 10 with carbodiimides 11 promoted by reagent 3 in the presence of triethylamine led to the formation of 4-imino beta-lactams 12 in good to excellent yields (scheme II).

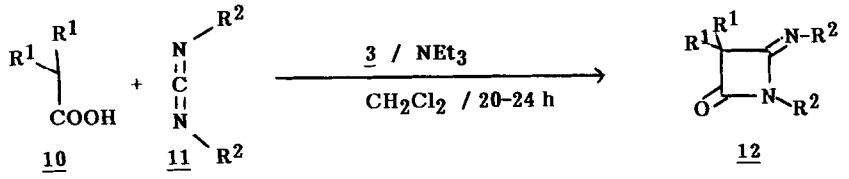
Scheme I



g R^1 = PhO R^2 = 4-$CH_3OC_6H_4$ R = H

h R^1 = PhO R^2 = 4-$CH_3OC_6H_4$ R = Ph

Scheme II



12a R^1 = Cl R^2 = c-C_6H_{11} 45% yield m.p. 77-79°C (lit. 80-81°C) [9a]

12b R^1 = Ph R^2 = c-C_6H_{11} 60% yield m.p. 158-161°C (lit. 161°C) [9b]

In conclusion the present method extends the use of the readily available reagents 3 and 4 to synthesize beta-lactams avoiding the use of acid chlorides as starting materials. Mild reaction conditions and good yields are noteworthy features of the method. Work is in progress in our laboratory for the use of compounds of type 6 as precursors of N-unsubstituted beta-lactams.

References and Notes

1.- Considered as Reagents and Synthetic Methods 48. A grant from Hezkuntza Saila of Eusko Jaurlaritza (Basque Government) and Ministerio of Educación y Ciencia to I. Ganboa and F.P. Cossío are gratefully acknowledged. This work was in part supported by GEMA S.A. (Spanish). We are grateful to BASF S.A. (Spanish) for financial support (supply of tripehnylphosphine).

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3.- For rewievs see : a) A.K. Mukerjee, R.C. Srivastava, Synthesis , 327 (1973); b) A.K. Mukerjee, A.K. Singh, Synthesis, 547 (1975); c) A.K. Bose, M.S. Manhas, Lect. Heterocycl. Chem. 3, 43(1976); d) N.S. Isaacs, Chem.Soc.Rev. 76 , 181(1976); e) A.K. Mukerjee, A.K. Singh, Tetrahedron , 1731 (1978); f) J.C. Sheehan, E.J. Corey, Org.Reac. 9 ,388(1975); g) M.S. Manhas, S.G. Amin, A.K. Bose, Heterocycles 5, 669 (1976).

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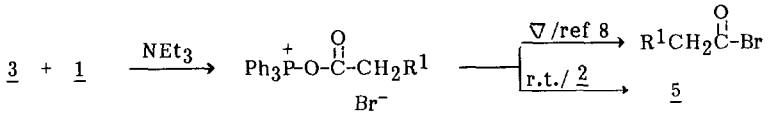
5.- While it would be premature to discuss the detailed mechanism, at this stage, a general pattern can be proposed. Under the conditions described reagent 3 reacts with carboxylic acids 1 to form an active intermediate which then reacts with the imine component 2 in the presence of base to give the four membered heterocycle 5.



6.- a) A. Arrieta, I. Ganboa, C. Palomo, Synthetic Commun. 14 , 939 (1984); b) Pyridinium bromide perbromide also can be used for carry out the bromination of 6h; conditions : reagent/substrate 1:1, AcOH, r.t., 1h, 70%.

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(Received in UK 25 April 1985)