Cyanuric Chloride: A Mild Reagent for β-Lactam Synthesis[1]

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Cyanuric chloride (**2**) is a low-priced chemical that is employed extensively in the dye-stuff industry as a synthetic reagent. Recent publications show that this compound can also be utilized for preparing peptides[2] and macrocyclic lactones[3], and for deoxygenating sulfoxides[4]. We report that **2** is a useful reagent for the synthesis of β-lactams.

Cyanuric chloride (**2**) activates carboxylic groups through the formation of active esters. We have found that the reaction of an

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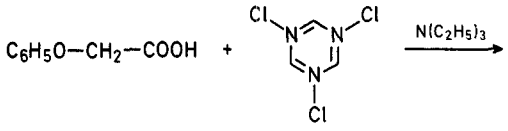
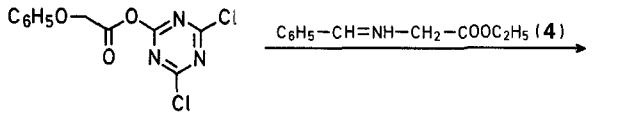
imino compound **4** with a substituted acetic acid (e.g. **1**) in the presence of **2** and triethylamine leads to β-lactams (e.g. **5**) in good yield.



1 **2**



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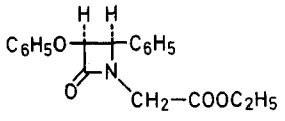

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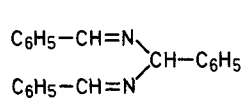
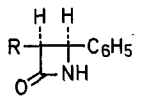
It is likely that the active ester **3** from **2** and the carboxylic acid **1** reacts with an azomethine **4** to form an acylimminium intermediate which undergoes internal Michael-type addition to produce a β-lactam. Alternatively, the active ester could first produce a ketene under the influence of triethylamine which then undergoes cycloaddition to the imino compound. The possibility of multiple pathways to β-lactams cannot be ruled out. Whatever be the exact mechanism, the important point is that the β-lactam formation is stereospecific in the cases we have studied: *cis*-β-lactams are formed from Schiff bases.

Cyanuric chloride has an advantage over some of the other activating agents employed for β-lactam synthesis: it is a stable reagent which can be used at room temperature or lower and the desired β-lactam is easy to isolate from the reaction mixture.

In one case, **2** appeared unsuccessful at first in producing a β-lactam: neither reaction of azidoacetic acid nor of phenoxyacetic acid and **2** led to a β-lactam by reaction with hydrobenzamide (α,α-dibenzylideniminotoluene; **6**) and triethylamine. However, β-lactam formation in good yield could be achieved by a modification of the reaction conditions, namely, by using the potassium salt instead of the free carboxylic acid. It seems that the free acid cleaves the hydrobenzamide even in the presence of triethylamine.



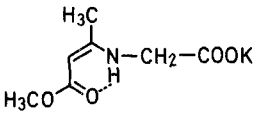
6



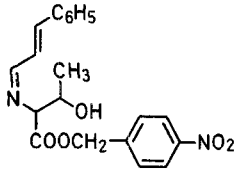
7a R = C_6H_5O
b R = N_3
c R = $C_6H_5O-CH_2-\overset{O}{\overset{\|}{C}}-NH$

Thus, the reaction of hydrobenzamide (**6**), potassium azidoacetate, **2**, and triethylamine in dry dichloromethane led to the azido-β-lactam **7b**[5] in 46% yield. It may be noted that the product obtained after the usual-work up including a dilute hydrochloric acid wash was the *N*-unsubstituted β-lactam. Reduction of the azido function in **7b** with Adams catalyst and hydrogen in ethanol followed by acylation with phenoxyacetyl chloride produced *cis*-3-phenoxyacetylamino-4-phenyl-2-azetidinone (**7c**) – a compound reported to show anti-penicillinase activity[6]. The original literature method for this compound involves reaction with either azidoacetyl chloride (a hazardous chemical) or with phthalimidoacetyl chloride (involves an extra step).

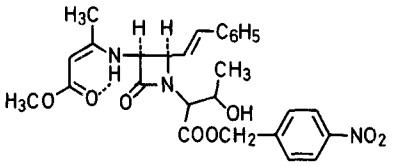
Recently, a non-hazardous synthesis of α-amido-β-lactams was reported from this laboratory[7,8] in which a Schiff base is treated with the glycine-derived "Dane salt" (**8**) in presence of ethyl carbonochloridate and triethylamine. We have found that the activation of the acid function in protected glycine salts can be provided with **2**. Thus, the reaction of the Schiff base **9**, derived from threonine *p*-nitrobenzyl ester and cinnamaldehyde, with Dane salt (**8**), **2**, and triethylamine at −20 °C afforded the *cis*-β-lactam **10**[9] in 40% yield. No protection of the hydroxy group of threonine was necessary in this reaction. The β-lactam **10** has been used as a key intermediate in the synthesis of 2-oxa- and 2-thia-1-dethiacephems and has been prepared earlier in this laboratory by an alternative synthesis[9].



8



9



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Melting points were determined in open capillary tubes using a "Mel-Temp" apparatus and are uncorrected. I.R. spectra were obtained with Perkin-Elmer Infracord and Perkin-Elmer 247 grating spectrometers. ^{1}H-N.M.R. spectra were recorded on a Varian EM 390 spectrometer in $CDCl_3$ solution containing tetramethylsilane as an internal standard. Mass spectra were obtained with a CIMS-Biospect (Scientific Research Instrument) mass spectrometer. Microanalyses were performed by Guelph Chemical Laboratories, Ontario, Canada.

***cis*-1-(Ethoxycarbonylmethyl)-3-phenoxy-4-phenyl-2-azetidinone (5):**
A suspension of cyanuric chloride (**2**; 1.84 g, 10 mmol) in anhydrous dichloromethane (30 ml) is added dropwise over 30 min to a stirred solution containing the Schiff base[10] **4** [prepared from benzaldehyde (1.06 g, 10 mmol) and ethyl glycinate (1.03 g, 10 mmol)], phenoxyacetic acid (**1**; 1.52 g, 10 mmol), and triethylamine (4.04 g, 40 mmol) in anhydrous dichloromethane (200 ml) at 0 °C under a nitrogen atmosphere. The mixture is stirred overnight, washed with water (100 ml), 5% sodium hydrogen carbonate solution (150 ml), brine (3 × 100 ml), and dried with magnesium sulfate. Evaporation of the solvent gives the crude title compound. Trituration of the crude product with 1:1 ethyl alcohol/ether affords the essentially pure compound **5**; yield: 1.89 g (58%); m.p. 85–87 °C (chloroform/ether).

$C_{19}H_{19}NO_4$	calc.	C 70.14	H 5.89	N 4.30
(325.4)	found	69.83	5.83	4.19

I.R. (Nujol): ν = 1750; 1740 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.22 (t, 3H); 3.45 (d, 1H, J = 18 Hz); 4.17 (q, 2H); 4.42 (d, 1H, J = 18 Hz); 5.18 (d, 1H, J = 5 Hz); 5.52 (d, 1H, J = 5 Hz); 6.6–7.3 ppm (m, 10H).

***cis*-3-Azido-4-phenyl-2-azetidinone (7b):**
To a mixture of hydrobenzamide (**6**; α,α-dibenzylideniminotoluene; 2.98 g, 10 mmol), potassium azidoacetate (1.39 g, 10 mmol), and triethylamine (3.03 g, 30 mmol) in dry dichloromethane (150 ml) cooled at 0 °C is added dropwise with stirring a suspension of cyanuric chloride (**2**; 1.84 g, 10 mmol) in dry dichloromethane (40 ml). The resulting mixture is stirred for 12 h at room temperature, then 10% hydrochloric acid (75 ml) is added. The precipitate which separates within 15 min is filtered and washed with ethanol (10 ml). Recrystallization from methanol/water gives the pure product; yield: 0.86 g (46%); m.p. 90–91 °C (Lit.[5], m.p. 90–91 °C).

***cis*-1-(1-*p*-Nitrobenzyloxycarbonyl-2-hydroxypropyl)-3-(1-methyl-2-methoxycarbonylvinylamino)-4-styrylazetidine-2-one (10)[9]:**
N-[1-Methyl-2-methoxycarbonylvinyl]-glycine potassium salt (**8**; 2.11 g, 10 mmol) is suspended in anhydrous dichloromethane (200 ml) to which

are added triethylamine (4.04 g, 40 mmol) and the imine **9** (3.68 g, 10 mmol; derived from cinnamaldehyde and threonine *p*-nitrobenzyl ester). The mixture is cooled to −20 °C under a nitrogen atmosphere. A suspension of cyanuric chloride (**2**; 1.84 g, 10 mmol) in anhydrous dichloromethane (30 ml) is added slowly dropwise with stirring. Following this addition, the mixture is maintained at −20 °C for 90 min and then at room temperature overnight. It is then washed with 5% sodium hydrogen carbonate solution (150 ml), brine (3 × 100 ml), dried with magnesium sulfate, and then evaporated under reduced pressure to afford the crude title compound. Trituration with 1:1 benzene/ethanol gives a white, solid compound, which is washed with ether (5 ml) and recrystallized from dichloromethane; yield: 2.09 g (40%); m.p. 148–150 °C.

$C_{27}H_{29}N_3O_8$	calc.	C 61.94	H 5.58	N 8.03
(523.5)	found	61.53	5.62	8.22

I.R. (Nujol): ν = 3400, 1730, 1725, 1650 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.30 (d, 3H); 1.95 (s, 3H); 3.53 (s, 3H); 3.85 (s, 1H); 4.44 (two q, overlap, 2H); 4.55 (d, 2H); 5.10 (dd, 1H, J = 5 Hz, J' = 9 Hz); 5.30 (s, 2H); 6.15 (dd, 1H, J = 9 Hz, J' = 16 Hz); 6.80 (d, 1H, J = 16 Hz); 7.20–7.45 (m, 5H); 7.60 (d, 2H, J = 9 Hz); 8.20 (d, 2H, J = 9 Hz); 9.15 ppm (d, 1H, J = 9 Hz).

C.I.M.S: m/e = 524 ($M^+ + 1$).

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[1] (a) Part 61 in the series "Studies on β-Lactams". For part 60 see A. K. Bose et al., *J. Heterocycl. Chem.*, in press.
(b) Presented in part at the 14th Middle Atlantic Regional Meeting, American Chemical Society, King of Prussia, Pennsylvania, April 1980.

[2] K. Venkataraman, D. R. Wagle, *Tetrahedron Lett.* **1979**, 3037.

[3] K. Venkataraman, D. R. Wagle, *Tetrahedron Lett.* **1980**, 1893.

[4] G. A. Olah, A. P. Fung, B. G. B. Gupta, S. C. Narang, *Synthesis* **1980**, 221.

[5] J. N. Wells, R. E. Lee, *J. Org. Chem.* **34**, 1477 (1969).

[6] J. M. Z. Gladych, C. W. T. Hussey, *German Patent* 2122747; *C.A.* **76**, 72389 (1972).

[7] A. K. Bose et al., *Synthesis* **1979**, 543.

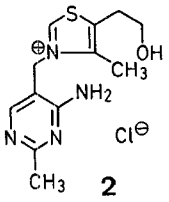
[8] A. K. Bose et al., *Tetrahedron Lett.* **1979**, 2771.

[9] A. K. Bose et al., Second International Symposium on Recent Advances in the Chemistry of β-Lactam Antibiotics, Cambridge, U.K., 1980.

[10] Y. Ogata, A. Kawasaki, H. Suzuki, H. Kojoh, *J. Org. Chem.* **38**, 3031 (1973).

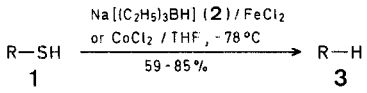
Errata and Addenda 1981

K. Karimian, M. Askari, M. Farahani, N. Sachinvala, *Synthesis* **1981** (1), 48–49:
The structure of compound **2** should be:

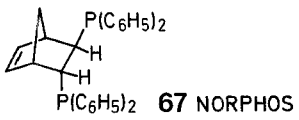


2

Abstract 5979, *Synthesis* **1981** (1), 79:
The formula scheme **1**→**3** should be:



V. Čaplar, G. Comisso, V. Šunjić, *Synthesis* **1981** (2), 85–116:
The correct name for compound **10** (p. 90) is 2,3-*O*,*O*-isopropylidenedioxy-1,4-bis[diphenylphosphino]butane (DIOP).
The structure of compound **67** (p. 103) should be:



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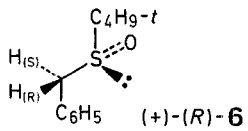
F. Sączewski, H. Foks, *Synthesis* **1981** (2), 154–155:
The correct names for compounds **6a**, **6b**, and **8** are 1(5)-Methyl-2,3,6,7-tetrahydro-8a*H*-pyrido[1,2-*a*]diimidazo[1,2-*c*: 1′,2′-*e*][1,3,5]triazinium Iodide **(6a)**, 1(5),11-Dimethyl-2,3,6,7-tetrahydro-8a*H*-pyrido-[1,2-*a*]diimidazo[1,2-*c*:1′,2′-*e*]triazinium Iodide **(6b)**, and 2,3,6,7-Tetrahydro-8a*H*-isoquino[2,1-*a*]diimidazo[1,2-*c*: 1′,2′-*e*][1,3,5]triazine Hydrochloride **(8)**.

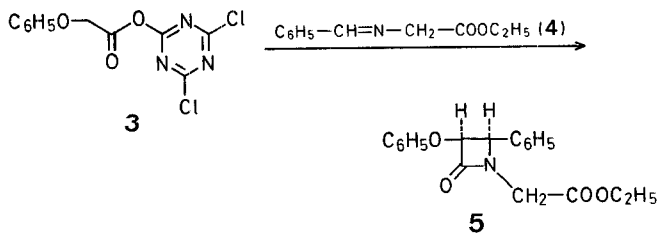
V. Aggarwal, A. Kumar, H. Ila, H. Junjappa, *Synthesis* **1981** (2), 157–158:
The substituents X^2—R for compounds **2g** and **3g** (p. 158) should be —NH—CH_2—CH_2—.

G. Solladié, *Synthesis* **1981** (3), 185–196:
The structure of compound **6** (p. 191) should be:

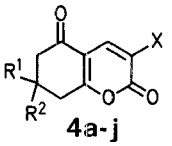


(+)-(*R*)-**6**

M. S. Manhas, A. K. Bose, M. S. Khajavi, *Synthesis* **1981** (3), 209–211:
The formula scheme **3**→**5** (p. 210) should be:

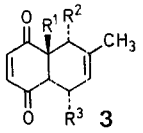


I. Trummer, E. Ziegler, O. S. Wolfbeis, *Synthesis* **1981** (3), 225–227:
The structure of products **4a–j** (p. 225) should be:



4a-j

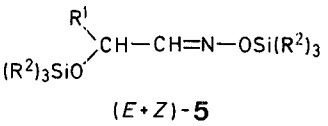
Abstract 6027, *Synthesis* **1981** (3), 243:
The structure of product **3** should be:



3

Abstract 6069, *Synthesis* **1981** (4), 332:
The title should be **2-Acylamino-β-lactams (3-Acylamino-2-oxoazetidines)**

H. Feger, G. Simchen, *Synthesis* **1981** (5), 378–379:
The correct name and structure of compounds **5** should be:

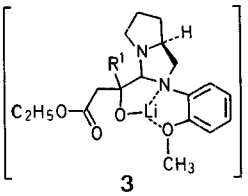


(*E*+*Z*)-**5**

2-trialkylsilyloxyalkanal *O*-trialkylsilyloximes [see H. Emde et al., *Synthesis* **1982** (1), p. 13 and 14]. The ^{1}H-N.M.R. assignments in the Table (p. 379) should be corrected accordingly.

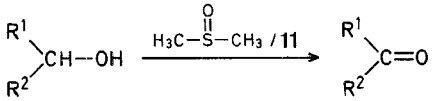
Abstract 6079, *Synthesis* **1981** (5), 403:
The title should be **Regioselective Alkoxycarbonylaminomethylation of Silyl Enol Ethers.**

Abstract 6098, *Synthesis* **1981** (5), 409:
The structure of intermediate **3** should be:

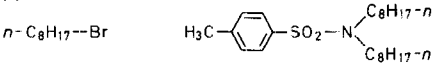


3

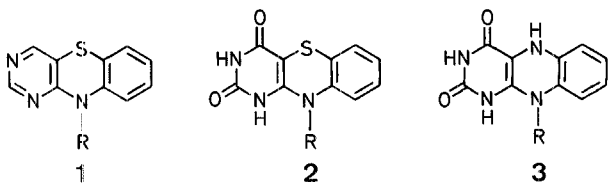
A. Akelah, *Synthesis* **1981** (6), 413–438:
The formula scheme, p. 419 right-hand column, should be:



G. Isele, J. A. Martinez, G. Schill, *Synthesis* **1981** (6), 455–457:
The substrate and product in entry 11 of the Table (p. 456) should be:



Y. Maki, M. Sako, M. Tanabe, M. Suzuki, *Synthesis* **1981** (6), 462–464:
The formula scheme (p. 462) should be:



1 **2** **3**