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RECENT DEVELOPMENTS IN β-LACTAM SYNTHESIS BY FOUR COMPONENT CONDENSATION

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According to recent literature the interest in β-lactams is still on the increase[1], partly because of the great variety of challenging chemical problems their synthesis poses, partly due to their often exquisite antibiotic properties and low toxicities.

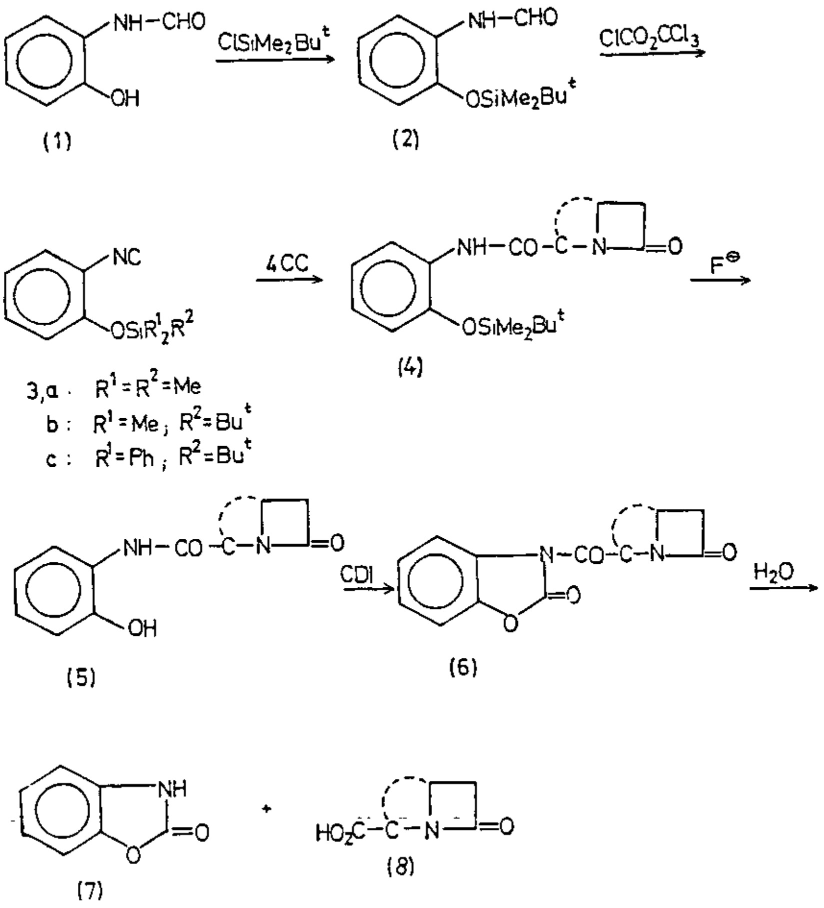
As a synthetic principle, the four component condensation[2,3] is almost ideally suited for the synthesis of β-lactams[6,7]. Generally Baeyer strain and conformational effects impede very much the formation of four-membered rings by cyclization of acyclic molecules. Thus it is quite difficult to convert β-amino acids into β-lactams[8], whereas β-lactams are formed with great ease by four component condensation. The intermediacy of a seven-membered cyclic α-adduct, e.g. (11), is probably responsible for the facile conversion of β-amino acids into β-lactams by four component condensation.

With four component condensations available, the accents in β-lactam synthesis have changed. When other methods are used to generate the four-membered ring, the latter step is the dominating issue in β-lactame syntheses, while with four component condensations the preparation of precursors and the subsequent selective cleavage of the amide groups which originates from the isocyanide represent the main problems[8,9].

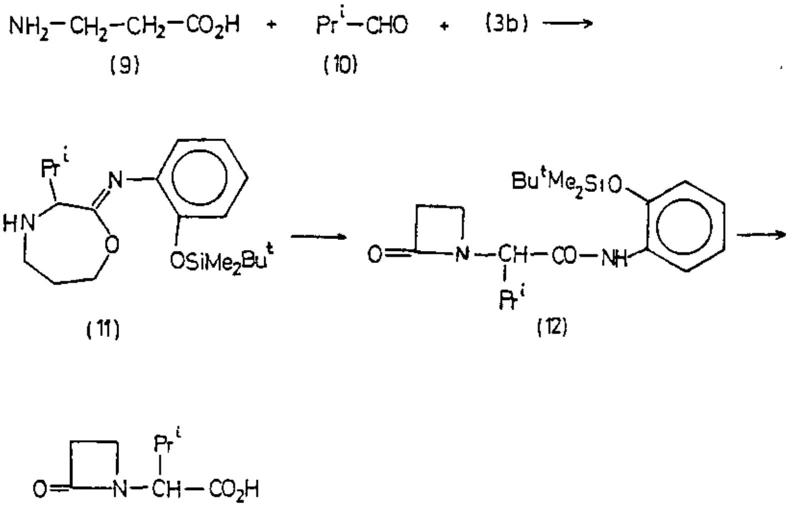
Since none of the traditional methods[10-12] is generally applicable and satisfactory for the aforementioned selective cleavage of amides, we have conducted a systematic search[13,14] for reactions and reagents which could be useful here. We found that certain o-substituted phenyl isocyanides lead to the formation of a carbonamide group that can be selectively cleaved in the presence of a β-lactam system[14]. With the knowledge that some o-substituted phenyl isocyanides are, in principle, particularly suitable for the solution of the above problem, we were looking for o-substituted phenyl isocyanide which is easy to obtain and easy to use in β-lactam synthesis as well as the subsequent selective amide cleavage.

We found that (3) serves our purpose particularly well.

Its preparation and use are illustrated by the following sheme.



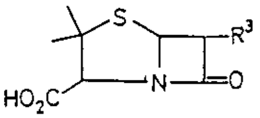
We observed that among the o-silyloxyphenylisocyanides (3) only (3b) is satisfactory for the given purpose; (3a) loses its TMS groups partially under 4CC conditions, and 3c is not sufficiently soluble in the solvents that are used for 4CC. The isocyanide (3b) is best prepared from (1)[15] by a one-pot-synthesis in which (1) in THF/triethylamine is reacted with $ClSiMe_2Bu^t$ and then with diphosgene[16]. The 4CC of β-alanine (9) and isobutyraldehyde (10) yields (12) via (11).


$NH_2-CH_2-CH_2-CO_2H$ (9) + Pr^i-CHO (10) + (3b) ⟶

(11) ⟶ (12) ⟶

(13)

Desilylation of (12) followed by treatment with CDI yields (13). Presently an analogous synthesis of (17) is in progress at our laboratory.


14,a : R^3 = Me
b : R^3 = Phthalimido

EXPERIMENTAL

2-tert-butyldimethylsiloxyphenylisocyanide
2-tert-butyldiphenylsiloxyphenylisocyanide

30 g (0,2 mol) tert-butyldimethylsilylchlorid (55 g (0,2mol) tert-butyldiphenylsilylchlorid) in 50 ml dry THF are added slowly to a solution of 27,4 g (0,2 mol) 2-formamidophenol and 28 ml (0,2 mol) dry triethylamine in 300 ml dry THF, stirred for 5 h and finally refluxed for 1 h. Then 56 ml (0,4 mol) triethylamine are added and the suspension is cooled to -20°C. Then 12,6 ml (0,1 mol) diphosgene (perchloromethylformate) in 20 ml dichloromethane are added within 30 min. to the well stirred suspension which is still kept for 2 h at low temperatures. Finally a stream of ammoniak is passed for 3 min. then the suspension is evaporated in vacuo. The residue is chromatographed with petroleumether (40-80°C) through a layer of basic aluminiumoxide and evaporated.

2-tert-butyldimethylsiloxyphenylisocyanide
is obtained as a non-distillable red oil.

yield: 16,3 g (35 %)

^{1}H-NMR: 0,3 ppm (s) $Si(CH_3)_2$, 1,1 ppm (s) $C(CH_3)_3$,
6,77 - 7,47 ppm (m) ArH_4

IR: 2125 cm^{-1}

$C_{13}H_{19}NOSi$	found	67,42 C ,	8,32 H ,	6,08 N
	calc.	66,90 C ,	8,21 H ,	6,00 N

2-tert-butyldiphenylsiloxyphenylisocyanide
is recrystallized from dichloromethane/methanol.

yield: 39,4 g (55%)
mp.: 64 - 65°C
IR: 2125 cm^{-1}

$C_{23}H_{23}NOSi$	found	77,45 C ,	6,55 H ,	3,98 N
	calc.	77,27 C ,	6,48 H ,	3,92 N

2-trimethylsiloxyformanilide

To 17,8 g (0,13 mol) 2-formamidophenol in 30 ml dry THF 16,25 ml (0,08 mol) hexamethyldisilazane are added under N_2 and stirred for one day at 20°C. Refluxing for 1 h completes the reaction. Evaporation of the solvent is followed by distillation.

bp. (0,01 torr): 100 - 102°C
yield: 21,2 g (84,5%)

^{1}H-NMR ($CDCL_3$): 0,3 ppm (s) $-Si(CH_3)_3$, 6,7 - 7,3 ppm (m) ArH_4, 8,5 and 9,2 ppm (s) -NH-CHO

2-trimethylsiloxyphenylisocyanide[13]

A solution of 3,25 ml (25mmol) diphosgene in 5ml dichloromethane is added to 9,65 g (50mmol) 2-trimethylsiloxyformanilide and 10,1 ml (0,10mol) dry triethylamine in 50 ml dry dichloromethane at -40°C. Addition of dry ether, filtration and evaporation of the solvent are followed by distillation.

bp. (0,05 torr): 35°C
yield: 4,28 g (49%)
IR: 2125 cm^{-1} (s)

^{1}H-NMR ($CDCL_3$): 0,3 ppm (s) $-Si(CH_3)_3$, 6,7 - 7,3 ppm (m) - $-ArH_4$

Formation of (12) by four component condensation

The suspension of 720 mg (10mmol) isobutyraldehyde and 890 mg (10 mmol) β-alanine in 30 ml dry methanol is kept for 1 h under N_2 at 50°C. At 20°C 2,33 g (10 mmol) 2-tert-butyldimethylsiloxyphenylisocyanide are added and stirred for 3 days. After 2 days it is a clear solution. Evaporation and recrystallisation from hexane yield a corlorless crystalline product.

yield: 2,07 g (55%)
mp.: 73 - 74°C
IR (KBr): 3295 cm^-1 (m), 1750 cm^{-1} (s), 1660 cm^{-1} (s)

^{1}H-NMR ($CDCl_3$): 0,3 ppm (s) $Si(CH_3)_2$, 1,05 ppm (s) $C(CH_3)_3$
+ (d) $CH(CH_3)_2$, 2,03 - 3,73 ppm (dq)$CH(CH_3)_2$,
2,97 ppm (t) and 3,47 ppm (m) $-CH_2CH_2-$,
3,9 ppm (d) -CH-iPr, 6,73 - 7,3 ppm (m) ArH_4,
8,0 ppm (s) NHCO

$C_{20}H_{31}N_2O_3Si$	found	63,98 C	, 8,47 H	, 7,42 N
	calc.	63,96 C	, 8,32 H	, 7,46 N

Desilylation

In 20 ml dry THF 1,97 g 4 (5 mmol) are treated 3 h with 2,61 g (10mmol) anhydrous tetra-butylammoniumfluoride. After evaporation, the residue is dissolved in dichloromethane and washed two times with water, dried and evaporated in vacuo. Recrystallization of dichloromethane/hexane yields a grey powder, whose data are identical with an authentic sample, obtained from benzyloxyphenylisocyanide and hydrogenation[13,14].

yield: 1,25 g (90%)
mp.: 142-143°C

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2 The condensation of an amine and a carbonyl compound with a suitable acid or its anion and an isocyanide to yield an amino acid derivative is called a four component condensation. The term four component condensation is also used for those reactions in which fewer, or more than four components participate, if the reactants contain the functional groups which are characteristic of the four component condensations, or if the reactants correspond to pre-condensation products (e.g., the imines, enamines, aminals and hexahydro-1.3.5-triazines that are formed from amines and carbonyl compounds) "α-Additions of iminium ions and anions, followed by secondary reactions" and "Ugi reaction" are synonyms for "four component condensation".

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