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REGIOSELECTIVE SYNTHESIS OF (±)-GABACULINE HYDROCHLORIDE

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SUMMARY

3-Cyclohexenecarboxylic acid (2) has been functionalized to the protected amino acid 5 in a novel reaction sequence, the crucial step being the acid catalysed cyclization of the γ,δ-unsaturated isocyanate 3 to the bicyclic lactam 4. 5 was converted into gabaculine hydrochloride (1 • HCl).

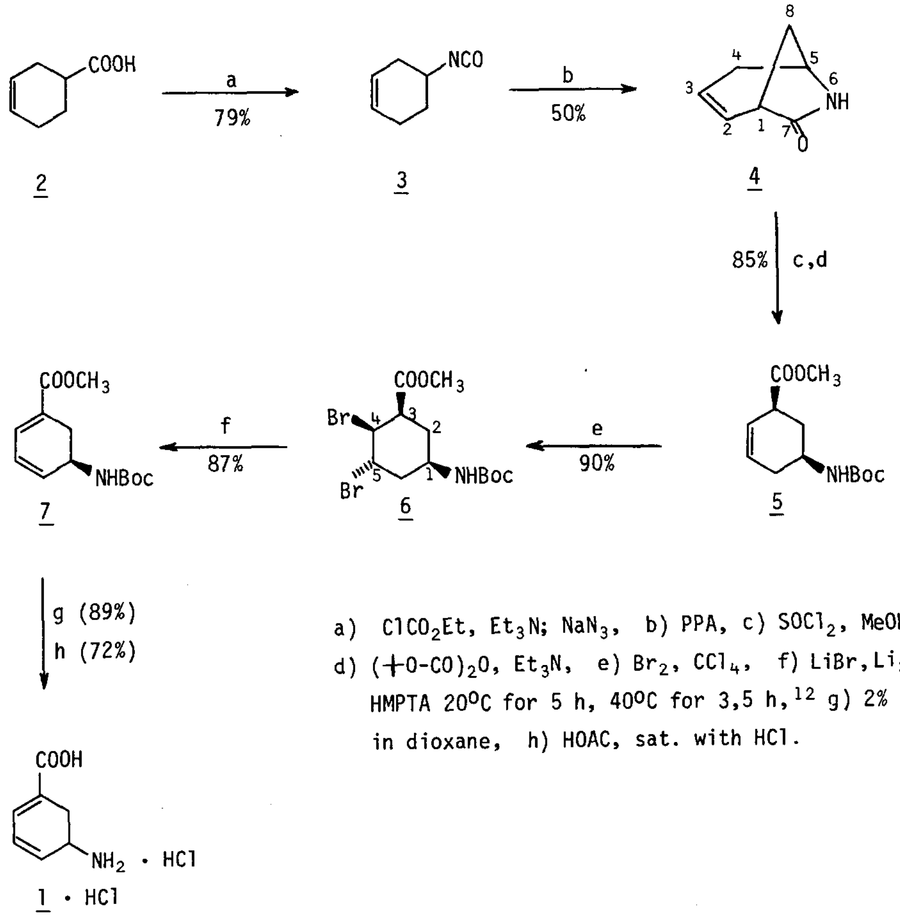
Gabaculine (1) has been isolated by Mishima et al.[1] from *Streptomyces toyocaensis*. 1 is a potent, irreversible inhibitor of γ-aminobutyric acid-α-ketoglutaric acid transaminase (GABA-T)[2]. Three syntheses of 1 have been reported so far[1,3,4] and iso-gabaculine has been prepared also[5].

Our strategy to synthesize 1 is based on our finding, that γ,δ and δ,ε-unsaturated isocyanates undergo an acid catalyzed cyclization to 5 and 6-membered lactams, respectively.[6]

3-Cyclohexene-1-carboxylic acid (2) (Scheme 1)[7] was converted to 1-isocyano-3-cyclohexene (3) in 78,5% yield by the ethylchloroformate-NaN_3-method[8]. Cyclization of 3 to 4 was carried out in PPA in 50% yield[9]. Treatment of 4 first with thionylchloride in CH_3OH and then with di-t. butyl-carbonate [10] gave the protected amino acid 5 (m.p. 55-56°C; 85%). Bromination-dehydrobromination to 7 worked satisfactorily. The stereochemistry of 6 (m.p. (pentane) 148-149°C) could be deduced from the NMR spectra: H(axial)-C(2) at 1,79 ppm, J(gem) $\sim$ J(2,1) $\sim$ J(2,3) $\sim$ 12Hz; H-C(3) at 3,48 ppm, J(3,2 axial) $\sim$ 12, J(3,2 equa.) $\sim$ J(3,4) $\sim$ 3Hz.

Finally the protecting groups were removed and gabaculine hydrochloride was isolated (after recrystallization from ethanol-ether, m.p. 197-200° (dec.)) which was identical in every respect (NMR, m.p., mixed m.p.) with an authentic sample[11].

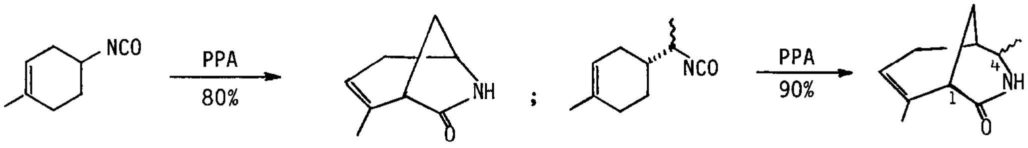
Scheme 1



a) ClCO$_2$Et, Et$_3$N; NaN$_3$, b) PPA, c) SOCl$_2$, MeOH, d) (+O-CO)$_2$O, Et$_3$N, e) Br$_2$, CCl$_4$, f) LiBr,Li$_2$CO$_3$, HMPTA 20°C for 5 h, 40°C for 3,5 h,[12] g) 2% NaOH in dioxane, h) HOAC, sat. with HCl.

Analogous treatment of 8 with PPA (Scheme 2) led to 9 (m.p. ($CHCl_3$, hexane) 77-79°C) in 80% yield. The substantially higher yield as compared to the reaction 3 → 4 suggests the importance of the C(4) alkyl substituent for the stabilization of the intermediate carbenium ion. Cyclization of (+)-10 (Scheme 2) which was prepared from the corresponding acid[13] revealed another aspect of the reaction under the employed conditions (PPA). The lactam 11 was formed in 90% yield as a racemic ca. 1:1 endo-exo mixture; in the NMR spectrum the d-s at 1,24 and 1,14 ppm (CH_3-C(4)) splitted into two d-s each upon addition of Eu $(hfc)_3$.

Scheme 2



8 9 (+)10 rac. 11

This proves , that in this case the protonation and deprotonation of the double bond is faster than the cyclization.

References and Notes

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[4] B.M. Trost & E. Keinan, ibid. 44, 3451 (1978).

[5] S. Danishefsky & F. Hershenson, ibid. 44, 1180 (1978).

[6] Cyclization of aromatic isocyanates are well known, e.g. S. Ohta & S. Kimoto, Chem. Pharm. Bull. 24, 2969 (1976).

[7] All compounds gave satisfactory elemental analyses and displayed NMR and IR spectra in agreement with their structures.

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[9] 70 g of 3 were stirred into 350 mℓ of PPA, whereupon the temperature quickly rose to 100°C. After ca. 10 minutes, the reaction was over and the mixture became homogeneous. Workup with water and chloroform and subsequent crystallization from methylenechloride-t-butylmethylether furnished 35 g 4 (m.p. 97°C). NMR. (400 MHz, $CDCl_3$)δ: 6,15-6,07 (dxdxm; J(2,3)∿9, J(2,1)∿8; H-C(2)), 5,91-5,8 (broad s; ≥NH), 5,69-5,62 (dxm; J(3,2)∿9; H-C(3)), 3,88-3,82 (m; H-C(5)), 2,77-2,72 (dxd; J(1,2)∿8; J(1,8)∿5; H-C(1)), 2,41 (dxm; J(4,4')=18, H-C(4)), 2,29 (dxdxd; J(8,8')=10, J(8,1)∿5; J(8,5)∿4; H-C(8)), 2,16 (dxm; H'-C(4)), 1,81 (d, H(8',8)=10; H'-C(8)). In the reaction mixture cyclohexadiene has been detected qualitatively (GLC).

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[11] Thanks are due to Dr. H. Mishima for sending us a sample of gabaculine hydrochloride.

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