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A NEW SYNTHETIC METHOD FOR PREPARATION OF 1,3,4,5-TETRAHYDRO-2H-1-BENZAZEPIN-2-ONE DERIVATIVES

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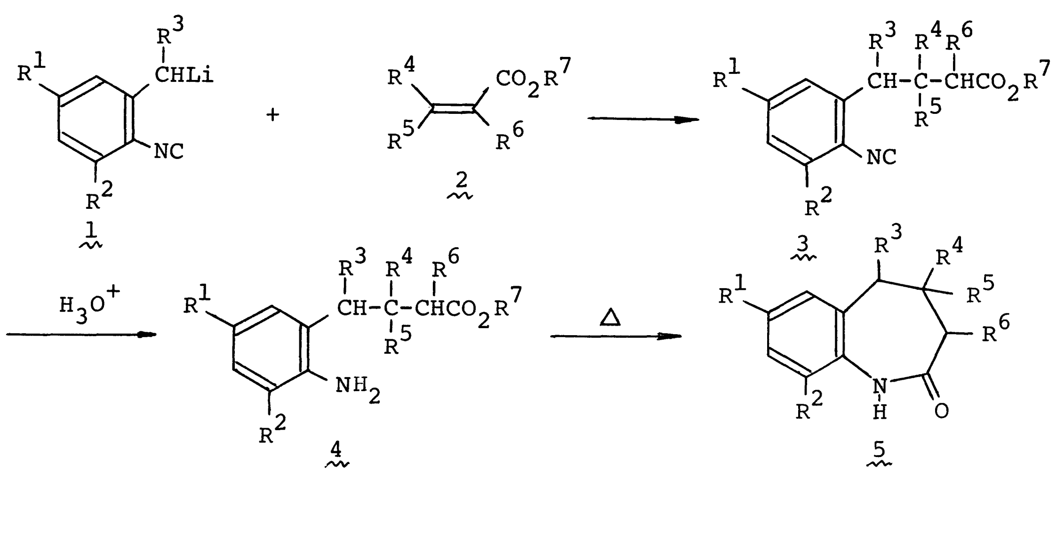
A 1,4-addition reaction of o-lithiomethylphenyl isocyanide to α,β-unsaturated carboxylic acid esters gives, after acid hydrolysis, γ-(o-aminophenyl)butyric acid esters, which are heated at 180°C to afford 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one derivatives.

In the preceding papers[1)] we described that o-lithiomethylphenyl isocyanide (1) generated in situ at -78°C from o-tolyl isocyanide and lithium diisopropylamide (LDA) is an useful intermediate for syntheses of indoles and the related heterocycles. Herein, we wish to report a general and convenient synthetic method for preparation of 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one derivatives (5) (5,6-benzo-ε-caprolactams) starting with o-tolyl isocyanide. The synthesis of 5 involves a 1,4-addition[2)] of 1 to α,β-unsaturated carboxylic acid esters as a key step, producing γ-(o-isocyanophenyl)butyric acid esters, which are hydrolyzed with aq HCl to give γ-(o-aminophenyl)butyric acid esters, as shown in Scheme 1.

Scheme 1



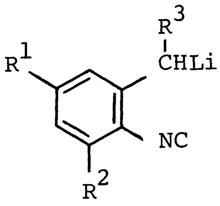
A general procedure for the preparation of 5 is illustrated as follows. To a deep red solution of o-lithiomethylphenyl isocyanide (1a) in diglyme, which had been prepared at -78°C by treatment of 351 mg (3 mmol) of o-tolyl isocyanide with LDA (6 mmol) in 8 ml of diglyme according to the reported procedure,[1a) 601 mg (6 mmol) of methyl crotonate was added at once. The deep red color of 1a immediately turned to light yellow. The reaction mixture was quenched with aq. NH_4Cl and extracted with ether. The ether extract was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was distilled using Kugelrohr to afford methyl γ-(o-isocyanophenyl)-β-methylbutyrate (3a-i) in an 87% yield (bp 138-140°C/0.1 mmHg) [3a-i : IR (neat) 2120, 1735 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.00 (d, 3H), 2.30 (m, 2H), 2.40 (m, 1H), 2.74 (m, 2H), 3.68 (s, 3H), 7.33 (s, 4H)].[4) Next, 3a-i (521 mg, 2.40 mmol) was added to 2% HCl in 1:1 methanol-water (20 ml) and stirred for 1 hr at room temperature. The reaction was monitored by the disappearance of IR absorption band ($\nu_{N\equiv C}$) characteristic of the isocyano group in the reaction mixture. The resulting solution was made alkaline with 10% aq. NaOH and extracted with ether. The extract was distilled to furnish methyl γ-(o-aminophenyl)-β-methylbutyrate (4a-i) in an 85% yield (bp 135-137°C/0.1 mmHg) [4a-i : IR (neat) 3450, 3371, 1730, 1630 cm^{-1} ; NMR ($CDCl_3$ with Me_4Si) δ 0.95 (d, 3H), 1.88-2.90 (m, 5H), 3.60 (s, 3H), 3.83 (broad, 2H), 6.38-7.38 (m, 4H)]. Finally, 4a-i was heated at 180°C for 5 hr under slightly reduced pressure and, then, chromatographed on silica gel to afford 4-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (5a-i) in an 83% yield (mp 120-121°C) [5a-i : IR (KBr disk) 3180, 1665 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.08 (d, 3H), 1.80-3.08 (m, 5H), 6.75-7.28 (m, 4H), 8.58 (broad 1H)].[5)

2,4-Xylyl isocyanide (1b), 2,6-xylyl isocyanide (1c) and o-ethylphenyl isocyanide (1d) can be used in place of 1a in the above procedure, producing the corresponding substituted 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one derivatives. Some syntheses of 1,3,4,5-tetrahydro-2H-1-benzazepin-2-ones are summarized in Table 1.

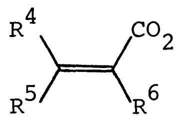
An asymmetric 1,4-addition of 1 with the crotonate of (-)-menthol resulted in only low optical yield of the 1,4-adduct, e.g., the reaction of 1a with the menthyl crotonate followed by hydrolysis and transesterification gave methyl γ-(o-aminophenyl)-β-methylbutyrate in 22% ee,[6) $[\alpha]_D^{21}$ -8.5°C ($CHCl_3$) (83% yield).

Preparation of 1,3,4,5-tetrahydro-2H-1-benzazepin-2-ones has been hitherto performed through Beckmann rearrangement[7) and Schmidt rearrangement[8) starting

Table 1. Syntheses of 1,3,4,5-Tetrahydro-2H-1-benzazepin-2-ones



1



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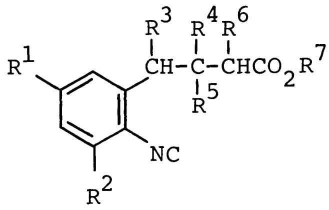

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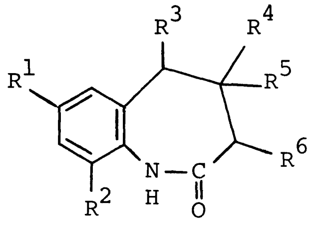

5

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)[a]		Yield (%)[b,c]	
H	H	H(1a)	H	Me	H	Me	87	(3a-i)	70	(5a-i)
H	H	H(1a)	H	H	H	Et	27	(3a-ii)[d]	76[e]	(5a-ii)
H	H	H(1a)	H	Me	Me	Et	41	(3a-iii)	56[f,g]	(5a-iii)
H	H	H(1a)	H	n-Pr	H	Me	~100	(3a-iv)	40	(5a-iv)
H	H	H(1a)	H	$-(CH_2)_4-$		Me	————		33[g,h]	(5a-v)
Me	H	H(1b)	H	Me	H	Me	73	(3b)	77	(5b)
H	Me	H(1c)	H	Me	H	Me	85	(3c)	80	(5c)
H	H	Me(1d)[i]	H	Me	H	Me	89	(3d)	42[g]	(5d)

a) Isolated yields. b) Isolated overall-yield based upon 3.

c) The cyclizations of 4 to 5 were carried out by heating at 180°C for 5 hr unless otherwise noted.

d) Polymerization of ethyl acrylate occurred concurrently.

e) The cyclization : 180°C, 6 hr. f) The cyclization : 220°C, 4 hr.

g) A mixture of diastereoisomers. h) The yield is based upon 1a.

i) 1d was generated in situ at -78°C by treatment of o-ethylphenyl isocyanide with lithium 2,2,6,6-tetramethylpiperidide.

with α-tetralone derivatives. The present method has a great advantage in that the starting materials, o-toluidines and α,β-unsaturated esters, are readily available, and consequently a wide variety of 1,3,4,5-tetrahydro-2H-1-benzazepin-2-one derivatives can be prepared.

References and Notes

1) a) Y. Ito, K. Kobayashi, and T. Saegusa, J. Am. Chem. Soc., 99, 3532 (1977).
b) Y. Ito, K. Kobayashi, and T. Saegusa, Tetrahedron Lett., 2087 (1978).
c) Y. Ito, K. Kobayashi, and T. Saegusa, Tetrahedron Lett., 1039 (1979).
d) Y. Ito, K. Kobayashi, and T. Saegusa, J. Org. Chem., 44, 2030 (1979).
e) Y. Ito, K. Kobayashi, N. Seko, and T. Saegusa, Chem. Lett., 1273 (1979).

2) N,N-Dimethyl crotonamide reacted with o-lithiomethylphenyl isocyanide to give the 1,4-adduct, N,N-dimethyl γ-(o-isocyanophenyl)-β-methylbutyramide, in an 84% yield. On the other hand, α,β-unsaturated ketones and aldehydes reacted with o-lithiomethylphenyl isocyanide to afford the 1,2- and/or 1,4-adducts, depending upon the structure of the carbonyl compounds.[3)]

3) Y. Ito, K. Kobayashi, and T. Saegusa, to be published.

4) 3a-iii (bp 140°/0.1 mmHg) : IR (neat) 2125, 1730 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.85 (d, 3H), 1.18 (d, 3H), 1.22 (t, 3H), 1.98-2.93 (m, 3H), 3.08-3.55 (m, 1H), 4.00 (q, 2H), 7.20 (s, 4H).
3d (bp 125°/0.1 mmHg) : IR (neat) 2125, 1740 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) four doublets at 0.83, 1.00, 1.23 and 1.28 (combined 6H), 1.88-3.18 (m, 4H), three singlets at 3.69, 3.74 and 3.76 (combined 3H), 6.88-7.35 (m, 4H).

5) 5a-iii : IR (KBr disk) 3180, 1668 cm^{-1}; NMR ($CDCl_3$) δ 0.95-1.28 (m, 6H), 1.90-3.28 (m, 4H), 6.83-7.38 (m, 4H), 7.95 (broad, 1H).
5a-iv (sublimates at 202-204°C) : IR (KBr disk) 3185, 1670 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.99-2.94 (m, 12H), 6.87 (broad, 1H), 7.44 (m, 4H).
5d : IR (KBr disk) 3190, 1670 cm^{-1}; NMR ($CDCl_3$) four doublets at δ 0.75, 1.24 1.28 and 1.38 (combined 6H), 1.80-2.88 (m, 4H), 6.85-7.45 (m, 4H), 8.98 (broad, 1H).

6) The optical yield was determined by NMR analysis using a shift reagent, tris-[d,d-dicamphonylmethanoate]europium.

7) a) G. Schroeter, Chem. Ber., 63, 1308 (1930).
b) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, J. Am. Chem. Soc., 74, 5153 (1952).

8) P. A. S. Smith, J. Am. Chem. Soc., 70, 320 (1948).

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