Tetrahedron Letters Vol. 21, pp 569 - 572 0040-4039/80/0201-0569$02.00/0

INTER VS INTRAMOLECULAR AMIDOALKYLATIONS OF AROMATICS - A NEW SYNTHESIS OF OXINDOLES, ISOQUINOLONES AND BENZAZEPINONES

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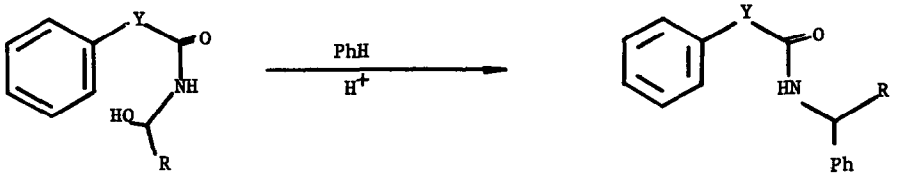
Summary: A new synthesis of oxindoles (8) isoquinolones (5) and benzazepinones (10) by the intramolecular amidoalkylation of aromatic amides of bismethoxycarbonylaminoacetic acid (4, 7, 9) is described.

Recently we have described a new synthesis of α-amino acids based on the amidoalkylation of aromatic, olefin and active methylene compounds with adducts of glyoxylic acid-primary amides[1]. During this investigation we were puzzled by the observation that the adduct of phenylacetamide



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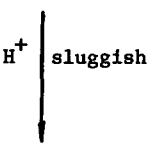
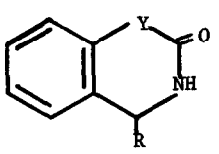


a, Y = CH_2; R=H
b, Y = CH_2; R=CO_2H
c, Y = CH_2; R=CCl_3
d, Y = CMe_2; R=CO_2H
e, Y = O; R=CO_2H
f, Y = NH; R=CCl_3



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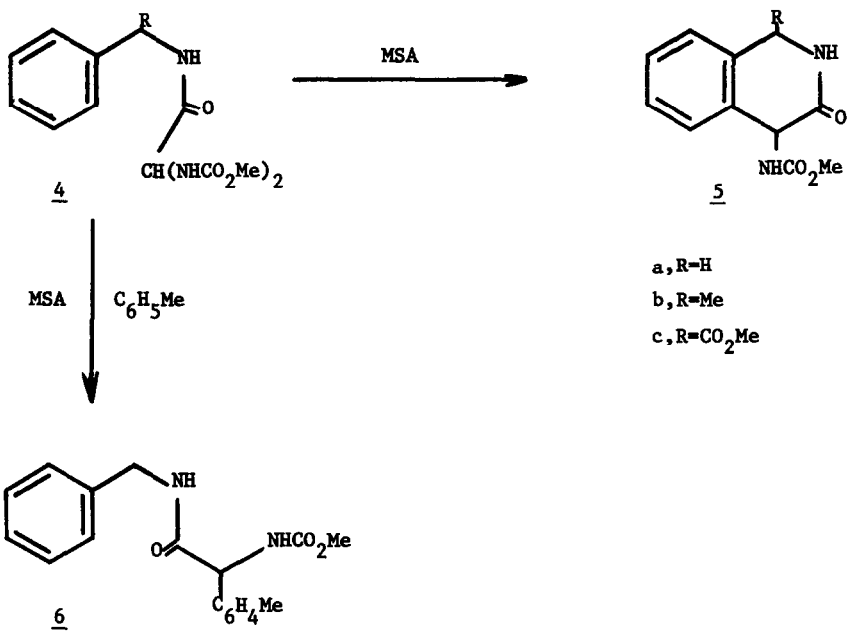
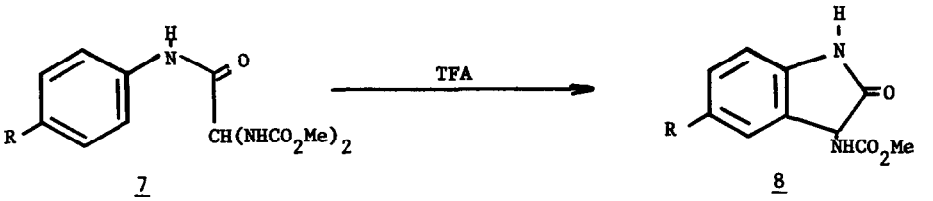
and glyoxylic acid 1b, reacted smoothly with benzene, in methanesulfonic acid at room temperature, in an intermolecular fashion to give the N-phenylacetylphenyl glycine (2b)[1] in 92% yield. We did not observe the formation of any isoquinolone (3b) which could have been the result of an intramolecular amidoalkylation. Furthermore, omitting the benzene, the external aromatic nucleophile, from the reaction mixture led to a bad mixture of polar products. The preferred intermolecular reaction was found to be rather general in a series of compounds of type 1. Thus formaldehyde[2] and chloral[3] adducts of phenylacetamide 1a and 1c also afforded N-benzylphenylacetamide (2a) and 2c in 73% and 82% yield. The adduct of α,α-dimethylphenylacet amide and glyoxylic acid behaved similarly and afforded the product of the intermolecular reaction when treated with benzene

(2d, m.p. 169° 80%). The gem-dimethyl did however improved the yield of the isoquinolone (3d) in the intramolecular reaction (35%, m.p. 213°). Substituting the methylene group of phenylacetamide for oxygen and using phenyl carbamate adduct 1e, or activating the phenyl ring of the phenylacetamide by a methoxy group in position 3 did not improve the relative rate of the intramolecular reactions.

A more promising system, from the synthetic point of view, which afforded good intra and intermolecular amidoalkylation reactions is the aromatic amides of bismethoxycarbonylaminoacetic acids 4, 7 and 9. These amides are easily prepared from methyl carbamate, glyoxylic acid and primary aromatic amines. Reacting the benzylamide 4a with toluene in MSA at room temperature gave the benzylamide 6 in 75% yield.



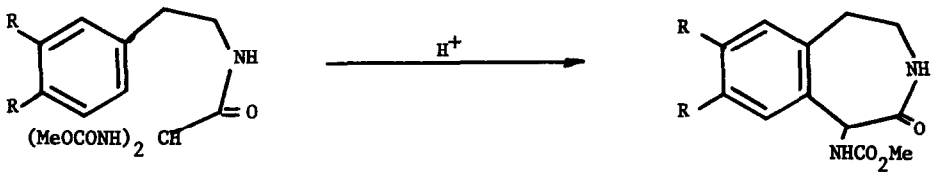
If toluene, the external aromatic nucleophile, was omitted from the reaction mixture a smooth intramolecular cyclization occurred affording 4-methoxycarbonylamino-3-isoquinolone (5a) in 84% yield (m.p. 164°). Even in the presence of benzene the main product was the cyclic isoquinolone derivative 5a. Smooth cyclizations were also observed with 4b and 4c when treated with MSA at room temperature. The 1,4-disubstituted-3-isoquinolones 5b (83%) and 5c (85%) were obtained as mixture of two isomers. The major isomer 5b (m.p. 193-194°) was purified on a florisil column. The major methyl ester 5c (oil) was hydrolyzed to the crystalline acid (m.p. 238-240° dec). This type of cyclization was further extended to the synthesis of oxindoles 8 and two benzazepinones 10:



7 8

a, R=H

b, R=Me



9 10

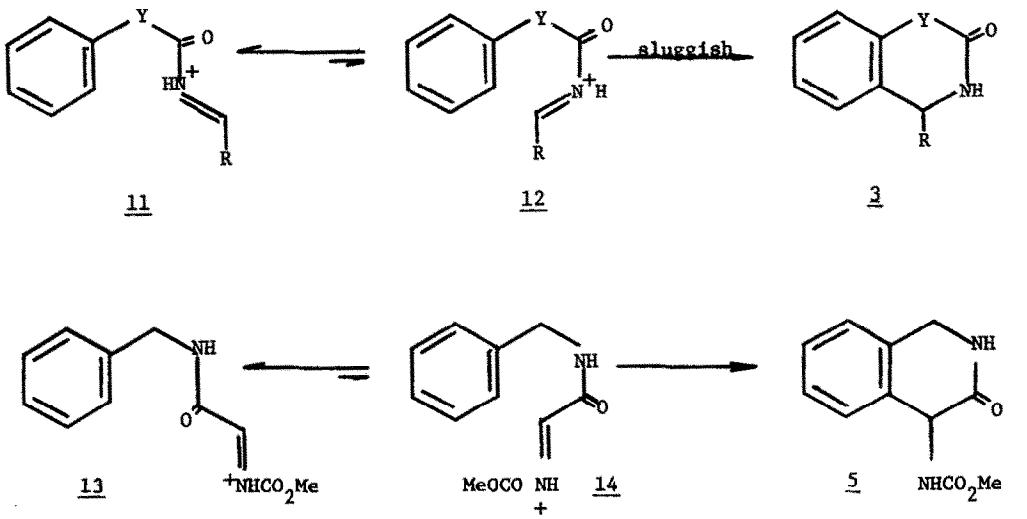
a, R=H

b, R=OMe

Cyclization of the anilide 7a in TFA at room temperature afforded 3-methoxycarbonylamino oxyindole 8a in 67% yield (m.p. 223-224°) accompanied by a more polar component which is probably the product of an intermolecular reaction. Treatment of the p-methyl derivative 7b with TFA at room temperature afforded the 3-methoxy carbonylamino-5-methyl-2-indolone (m.p. 232°) in 95% yield.

Two benzazepinones 10a (m.p. 214-216°,67%) and 10b (m.p. 230-231°, 64%) were also prepared by the cyclization of the corresponding amides of bismethoxycarbonylaminoacetic acid 9a and 9b in MSA and TFA respectively. The structures assigned to the reaction products are based on analytical data, NMR, IR and MS. All the cyclic products showed M^+ peaks and characteristic NMR spectra. The benzylic hydrogens α to the carbonyl group showed a doubled at 4.85 for the oxindoles, at 5.15 for the isoquinolone and at 5.91 ppm for the banzazepinone in DMSO-d_6.

One way of explaining the sluggish cyclization of 1 compared with the relative facile cyclizations of 4, is to look at the reactive intermediates in terms of Baldwins[4] rule for predicting the facilities of intramolecular cyclizations.



The preferred trans configuration of the amide group in both 11 and 13 explains the observed intermolecular reaction products in both cases. The difference between the two systems is the preferred cyclization of 14 compared with 12. If we assume that the main contributions to the mesomeric positively charged intermediates 12 and 14 are the ones described, we do have a favoured exo attack at the trigonal carbon of the carbon-nitrogen double bond in 14 while in 12 the attack at a similar carbon-nitrogen double bond is of the endo type and is therefore less favoured. This argument can be extended to explain the relative facile formation of the five and seven membered rings 8 and 10.

References

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(Received in UK 27 November 1979)