AMIDOALKYLATION OF AROMATIC COMPOUNDS WITH METHYLGLYOXAL-BISMETHYLCARBAMATE. A NEW SYNTHESIS OF 1-AMINO-1-PHENYL-2-PROPANONE DERIVATIVES AND SUBSTITUTED BENZOFURANS

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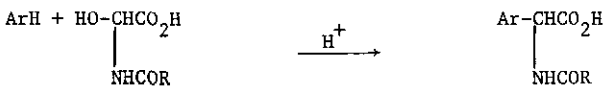
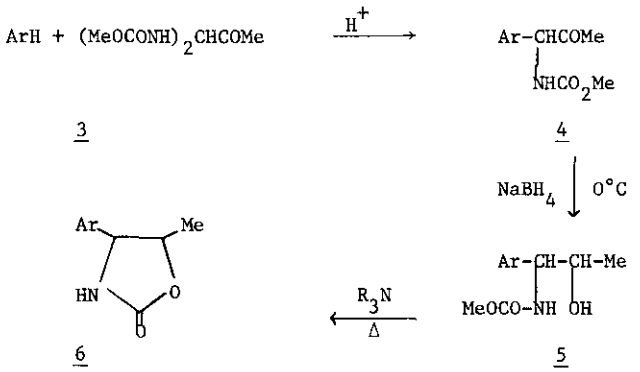
Abstract - The synthesis of 1-methoxycarbonylamino-1-aryl-2-propanones 4 and 3-methoxy carbonylamino-3-methylbenzofurans 7 by the direct amidoalkylation of aromatic compounds with methylglyoxal-bismethylcarbamate (3) is described. The amidopropanones (4) were further converted to the corresponding amido-propanols (5) and 2-oxazolidinones (6).

Adducts of glyoxylic acid-primary amides (1) are known to amidoalkylate aromatic compounds to give phenylglycine derivatives (2) in good yield:[1-6]



1 2

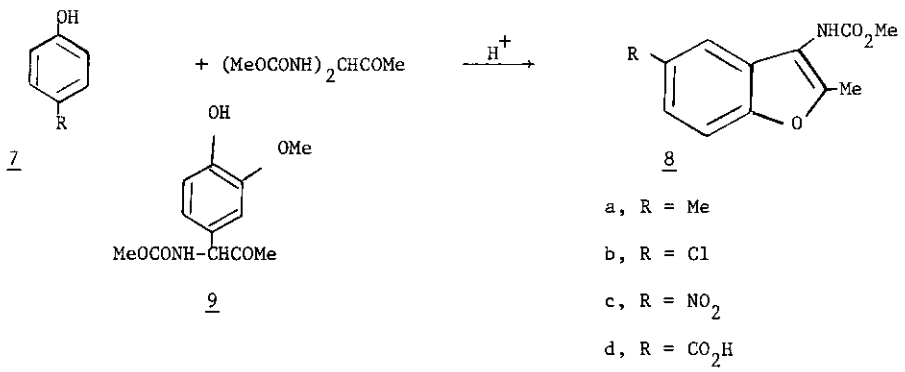
It was now found that if the adduct of glyoxylic acid (1) in the amidoalkylation reaction is substituted by the bisadduct of methylglyoxal and methylcarbamate (3) the above reaction can be extended to synthesise derivatives of 1-amino-1-phenyl-2-propanones:



3 4 5 6

a, Ar = Ph b, Ar = C_6H_4Me c, Ar = C_6H_4Cl

Thus, reacting methylglyoxal-bismethylcarbamate with benzene, toluene, p-xylene and chlorobenzene in concentrated sulfuric acid at room temperature for 24-48 h afforded the corresponding 1-methoxycarbonylamino-1-aryl-2-propanones (4) in 50-95% yield. The amidoalkylation of the reactive aromatic compounds: phenol, anisole, guaiacol, furan, and thiophene was carried out in methylene chloride solution and in the presence of various concentrations of methanesulfonic acid (see table). Monosubstituted aromatic compounds afforded crude products which were, according to their nmr spectrum, mixtures of ortho and para isomers. The para isomers which predominated were obtained pure on crystallization or chromatographic separation. Guaiacol gave practically only one product which according to an X-rays crystal structure analysis is compound 9.[7] para-substituted phenols (7) such as p-cresol, p-chlorophenol, p-nitrophenol and p-hydroxybenzoic acid afforded, when treated with methylglyoxal-bismethylcarbamate in acid media, the corresponding substituted 3-methoxycarbonylamino-2-methylbenzofurans (8) in good yields (see table):



7 9 8

a, R = Me

b, R = Cl

c, R = NO_2

d, R = CO_2H

Sodium borohydride reductions of three of the amidoketones 4 at 0 °C converted them to the correspondind arylpropanolamine derivatives 5 which on further heating in the presence of a tertiary base cyclized to the corresponding 2-oxazolidinone derivatives[8] 6. Sodium borohydride reduction at room temperature gave a mixture of the propanolamides 5 and the oxazolidinone 6. Both the propanolamides and the 2-oxazolidinones were obtained as mixtures of two isomers. Thus the 2-oxazolidinone 6a obtained by the reduction and cyclization of 4a was obtained as a mixture of cis-trans isomers. The major product according to an X-ray crystal structure analysis was the cis isomer.[9]

The amidoalkylating agent, methylglyoxale bismethylcarbamate (3), was prepared in 77% yield from methylglyoxal-dimethyl acetal and methyl carbamate in sulfuric-acetic mixture. It melted at 130 °C after crystallization from ethyl acetate-hexane. All new compounds gave appropriate microanalytical and spectral ir, nmr and mass) data.

Table: Amidoalkylation of Aromatics with 3.

Aromatic Compound ArH	Procedure	Product	Mp °C	Yield %
Benzene	A	4	oil	75%
Toluene	A	4	oil	50%
Chlorobenzene	A 48 h	4	oil	56%
p-Xylene	A	4	63	52%
Anisole	B	4	oil	64%
Phenol	C	4	99-101	70%
Guaiacol	B	9	82	67%
Furan	D	4	oil	34%
Thiophene	E	4	48	47%
p-Cresole	D	8a	133	56%
p-Chlorophenol	A	8b	158-160	58%
p-Nitrophenol	A	8c	197-198	56%
p-Hydroxybenzoic acid	A	8d	> 255	50%

A - 96% H_2SO_4; B - 1:1 (V:V) $MeSO_3H$:CH_2Cl_2; C - 10% H_2SO_4 in AcOH; D - 5% $MeSO_3H$ in CH_2Cl_2; E - 10% $MeSO_3H$ in CH_2Cl_2.

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7. Compound 9 melted at 82°C (ethyl acetate-hexane). It showed the following spectra: ir ($CHCl_3$): 3550 (OH), 3425 (NH) 1720 (CO) and 1500 cm^{-1} (NH); ^{1}H-NMR δ($CDCl_3$): 2.16 (3H, S, CH_3CO), 3.66 (3H, S, CO_2CH_3), 3.90 (3H, S, OCH_3), 5.25 (1H, d, J=6, Ar-CH-NH-), 6.83 (3H, S, ArH); MS ^{m}/e 253.0926 (5.2%).

8. M.E. Dyen and D. Suern, Chem. Rev., 1967, 67, 197.

9. The cis isomer (6a) was obtained pure by crystalline from ethyl acetate (mp 93°C). It showed the following spectra: ir ($CHCl_3$): 3440 (NH), 1750 cm^{-1} (CO); ^{1}H-NMR δ ($CDCl_3$): 0.92 (3H, d, J=6, CH_3), 4.80-5.18 (2H, m, CH-CH), 6.70 (1H, s (br) NH), 7.08-7.48 (5H, m, Ph); MS $^m/e$ 177.0785 (M^+ 24.4%).

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