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Further Studies on the Reaction of Unsaturated Acids with o-Phenylenediamine and 4-Substituted o-Phenylenediamines in Acid Medium

Mashooda HASAN, Shagufta MUNAWAR, Naeema KHAN
Department of Chemistry,
Quaid-i-Azam University, Islamabad-PAKISTAN
Zahida MAQBOOL
PINSTECH, Nilore-PAKISTAN

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Condensation of methylcrotonic acid with 4-chloro-o-phenylenediamine in 4N HCl yielded 5-chloro-2-(1-isobutenyl)benzimidazole and 7-chloro-4, 4-dimethyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one. Methacrylic acid when condensed with o-phenylenediamine in 4N HCl yielded the already reported 3-methyl-1,2,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one and 2(2-propenyl)benzimidazole. Condensation of methacrylic acid with 4-chloro-o-phenylenediamine in 4N HCl yielded 5-chloro-2(2-propenyl)benzimidazole. The structures of all the purified compounds were confirmed with the help of mass and ^{1}H NMR spectral analysis.

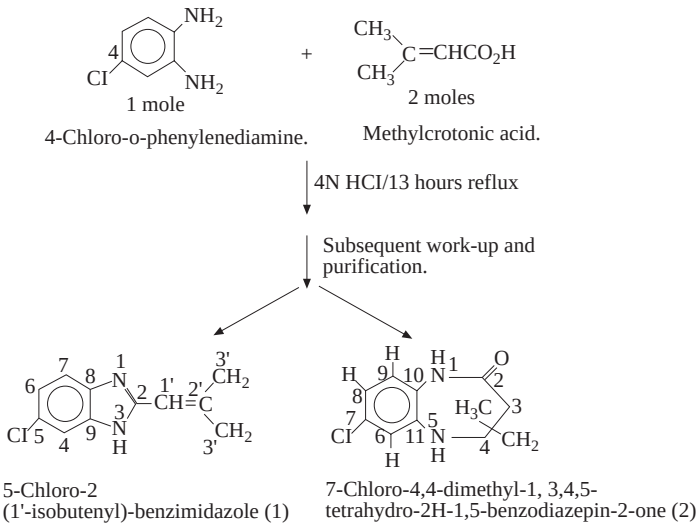
Introduction

Our previous work[1,2] on the condensation of various unsaturated carboxylic acids with o-phenylenediamine and 4-substituted o-phenylenediamines in the presence of 4N HCl has shown that the nature of aza-heterocycles formed in the reaction depends not only on the structure of the carboxylic acids used but also on the 4-substituent present in the o-phenylenediamines. As a result, of this work six new benzimidazoles having substituted vinyl side chains at 2-position and eight new substituted 1,2,4,5-tetrahydro-2H-1,5-benzodiazepines have been obtained. Benzimidazole derivatives are well known for their medicinal properties, such as anthelmintic, analgesic, anti-inflammatory, neuroleptic, antihistaminic and antineoplastic activities[3−6]. Polybenzimidazoles have been used as polymer material for fire resistant fibers with exceptional properties. Several benzodiazepines are useful psychotherapeutic agents. It was therefore considered worthwhile to carry out further reactions of unsaturated carboxylic acids with o-phenylenediamine and 4-substituted o-phenylenediamines in order to obtain some more new azaheterocyclic compounds.

Result and Discussion

Working on these lines, methylcrotonic acid was condensed with 4-nitro-o-phenylenediamine in 4N HCl under reflux. After the usual work up, the crude reaction mixture, which was obtained in the form of black tar, showed seven spots in TLC on silica gel plates, but no pure crystalline product could be separated from

the mixture. Methylcrotonic acid did not undergo any reaction with 4-chloro-o-phenylenediamine using 1:1 molar ratios of the reactants in 4N HCl under reflux. However, when the amount of methylcrotonic acid was doubled in the same experiment, the reaction occurred after thirteen hours of reflux. The crude reaction mixture obtained after the usual work-up showed three spots in TLC on silica gel using $CHCl_3$: MeOH (9:1). Column chromatography of the mixture on silica gel using n-hexane, ethyl acetate, methanol gradient gave two pure crystalline products which were identified as 5-chloro-2 (1-isobutenyl) benzimidazole (1) and 7-chloro-4, 4-dimethyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (2)(Scheme 1).

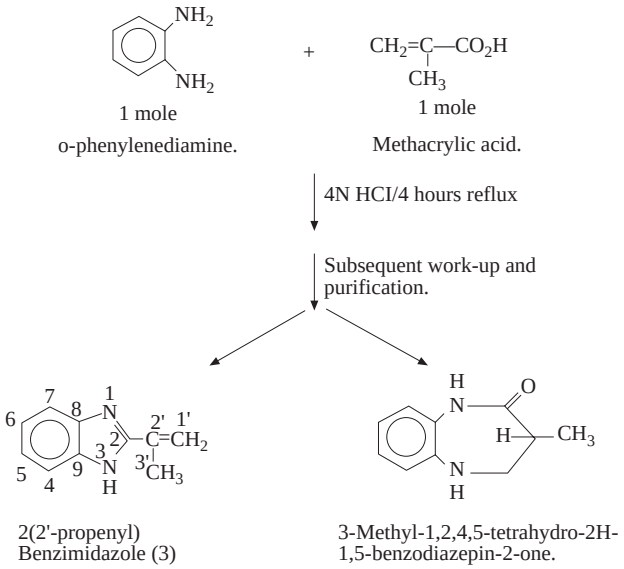


Scheme 1. Preparation of compounds 1 and 2.

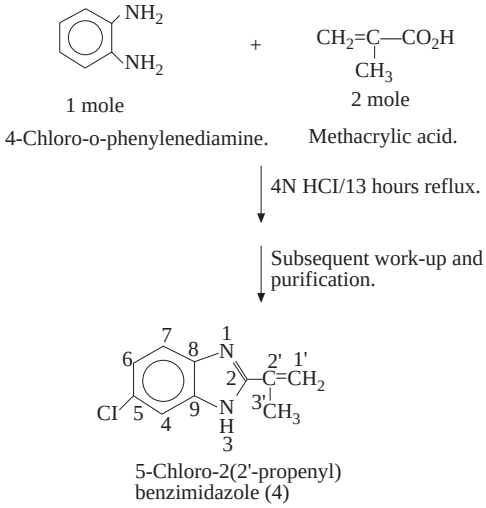
The next unsaturated carboxylic acid to be investigated was methacrylic acid, which was condensed with o-phenylenediamine in equimolar ratio in 4N HCl under reflux for four hours. The light brown solid obtained after usual work up showed two spots in TLC in $CHCl_3$. The compound having a lower R_f value was previously[2] obtained by the same reaction in pure form by recrystallization from $CHCl_3$ and was identified as 3-methyl-1,2,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one. The other compound exhibiting a higher R_f value could not be purified at that time. In the present study, the crude reaction mixture was recrystallized from methanol, whereby the already reported benzodiazepin crystallized out in pure form. The mother liquor was evaporated to dryness and the residue was recrystallized from acetone. A pure crystalline compound was obtained, which was identified as 2(2-propenyl) benzimidazole (3) (Scheme 2).

Methacrylic acid also failed to react with 4-chloro-o-phenylenediamine when the equimolar ratios of the two compounds were used. The reaction occurred when the molar ratio of methacrylic acid was doubled. The crude reaction product obtained after thirteen hours reflux and standard work up was subjected to column chromatography in n-hexane. One pure crystalline product was obtained which was identified as 5-chloro-2(2-propenyl) benzimidazole (4) (Scheme 3).

Details of the preparation, purification, physical properties and percentage yields of compounds 1-4 are given in the experimental. The structure of the purified compounds was determined with the help of their mass and ^{1}H NMR spectral analyses. Structure was assigned to each compound on the basis of the method of preparation and molecular ion peak. This structure was fully confirmed by ^{1}H NMR spectra where all chemical shifts and peak patterns were visible. Mass and ^{1}H NMR data of all the compounds are given in the experimental.



Scheme 2. Preparation of compound 3.



Scheme 3. Preparation of compound 4.

Experimental

Melting points were determined with "Electrothermal Series IA 9100 and IA 9200 Digital Melting Point Apparatus" and are uncorrected. EI MASS MAT was used for recording the mass spectra at H.E.J. Research Institute of Chemistry, University of Karachi, Karachi. NMR spectra were recorded with a 90 MHz, Jeol NMR spectrometer. All chemical shifts are given in ppm and refer to the δ scale relative to TMS. The signal multiplicities are abbreviated as s(singlet), d(doublet), dd(double doublet), t(triplet) and m(multiplet). E. Merck silica gel (35-70 mesh) was used for column chromatography. E. Merck precoated silica gel plates type 1.05554, were used for thin-layer chromatography. All solvents were distilled before use.

Compounds 1 and 2.

A mixture of 4-chloro-o-phenylenediamine (7.125g; 0.05 mole) and methylcrotonic acid (10g; 0.1 mole)

was refluxed for 13 hours in 75 ml 4N HCl with good stirring. The reaction mixture was then cooled and neutralized with sodium carbonate and extracted with chloroform. Chloroform was removed from the extract and the residue was chromatographed on a silica gel column using n-hexane, chloroform and methanol gradients.

5-Chloro-2(11-isobutenyl) benzimidazole (1).

Fractions eluted with n-hexane-chloroform (1:9) showing one single spot on TLC were combined. Solvent was removed and the residue was recrystallized from n-hexane to give 824 mg (8% yield) colourless crystals, melting at 133.7° C, R_f = 0.715 ($CHCl_3$-MeOH 9:1), MS: m/z (%) = 206(100), 205(16), 191(14), 166(37), 131(3), ^{1}H NMR (CD Cl_3): δ = 1.99 (d, 3H, 2-CH_3), 2.30 (d, 3H, 2^1-CH_3), 6.17 (m, 1H, 1 CH), 7.12 (d, 1H, 7-H), 7.52 (dd, 2H, 4-H and 6-H).

7-Chloro-4,4-dimethyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one (2).

Fractions eluted with chloroform-methanol (9:1) were combined after monitoring with TLC. The solvent was removed and the residue was recrystallized from chloroform as 2.9 g of colourless needles (26% yield), melting at 166.0° C. R_f = 0.503 ($CHCl_3$-MeOH, 9:1), MS : m/z(%) = 224(11), 208(1), 166(100), 131(20), ^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 6H, two 3-CH_3), 3.0 (s, 2H, 3-CH_2), 7.166 (dd, 1H, 8-H), 7.47 (d, 2H, 6-H and 9-H).

2(2-Propenyl) benzimidazole (3):

A mixture of methacrylic acid (4.32 g, 0.05 mole) and o-phenylenediamine (5.4g, 0.05 mole) was refluxed for 4 hours in 25 ml 4N HCl. Cooling and neutrelization yielded a brown solid which was filtered and dried. The crude product was found to be a mixture of two compounds when subjected to TLC in chloroform. Crystallization from methanol yielded 2.2g of a colourless compound melting at 207.1° C, R_f = 0.125 ($CHCl_3$), which was identified as the already reported 2-methyl-1,3,4,5-tetrahydro-2H-1, 5-benzodiazepin-2-one. Mother liquor was evaporated and the residue recrystallized from acetone, whereby 3.95g of a colourless compound melting at 250.7° C and showing R_f = 0.262 ($CHCl_3$) was obtained MS: m/z(%) = 158(100), 157(100), 143(31), 132(41), 118(24), ^{1}H NMR (CH_3OH): δ = 2.25 (dd, 3H, 3-CH_3), 5.45/5.95 (s/s, 2H, 1-CH_2), 7.2 (dd, 2H, 5-H and 6-H), 7.54 (dd, 4-H and 7-H).

5-Chloro-2(2-propenyl) benzimidazole (4):

A mixture of 4-chloro-o-phenylenediamine (7.125g, 0.05 mole) and methacrylic acid (8.6 ml, 0.1 mole) was refluxed in 75 ml 4N HCl for 13 hours. Black tar obtained after cooling and neutralization was extracted with chloroform. The extract was evaporated and the crude product was dried. The crude product was dissolved in a minimum amount of methanol and chromatographed on a silica gel column in n-hexane. A colourless compound was obtained which was recrystallized from n-hexane, melting at 171.7° C, yield 1.146g (11%). MS: m/z(%) 192(100), 191(63), 177(12), 166(21), 131(3), ^{1}H NMR ($CDCl_3$) δ = 2.3 (dd, 3H-3, -CH_3), 5.41/5.81 (s/s, 2H, 1-CH_2), 7.14 (d, 1H, 6-H), 7.46 (d, 1H, 7-H), 7.54 (s, 1H, 4-H).

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