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SYNTHESIS OF AMIDINE, IMIDATES ESTERS, OXADIAZOLES, IMIDAZOLES BANZIMIDAZOLE DERIVATIVES OF FACE 'C' ANNULATED 1,5-BENZODIAZEPINE

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ABSTRACT

It was thought of interest to synthesis 1,5 benzodiazepine substituted with isoxazole, and thiadiazole derivatives on its 2-position linked through oxyphenyl spacer. The conceived synthetic plan for the preparation of these materials proceeded through the acceptable protocol which emerged from the face 'c' cyclohexano substituted 1,5 benzodiazepine bearing the thiomethylether function on its 2-position is formed from the reaction of o-phenylenediamine with 2-oxoketenedithioacetal derivative of cyclohexanone. Its treatment with 2-aminobenzonitrile, p-hydroxy benzaldehyde and p-hydroxyacetophenone afforded the corresponding 2-amino substituted derivative of annulated 1,5-benzodiazepine, p-benzaldehyde and p-acetyl substituted derivatives. On its further reaction with 2-amino substituted derivative of annulated 1,5-benzodiazepine formed amidine and imidates esters derivatives which formed oxadiazoles, imidazoles benzimidazole derivatives of face 'c' annulated 1,5-benzodiazepine. The purity of the compounds was checked by TLC and their structures were established on the basis of their spectral data.

KEYWORDS:- 1,5benzodiazepine, o-phenylenediamine(OPD), 2-aminobenzonitrile, amidine and imidates esters etc

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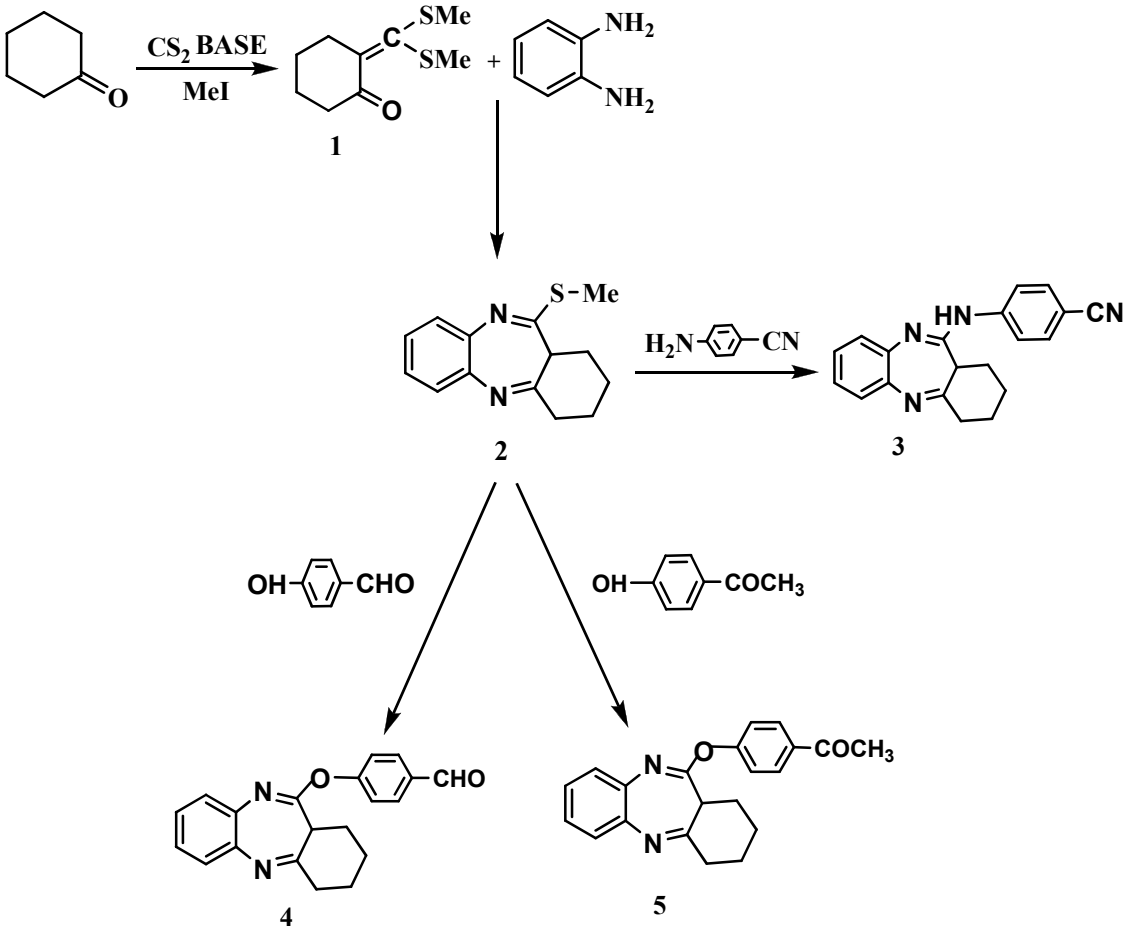
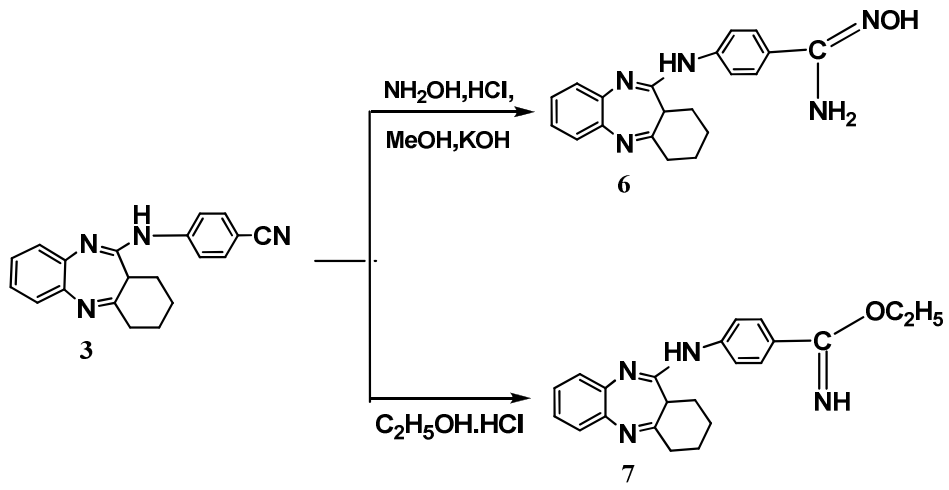
INTRODUCTION

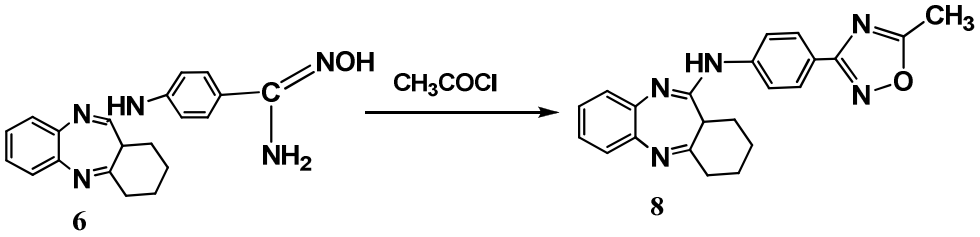
Benzodiazepines have attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. It constitute an important class of psychopharmaca,[1] in particular as tranquilizers and also as potent virucides and non-nucleoside inhibitors of HIV-1 reverse transcriptase.[2] 1,5-benzodiazepines has a great importance in biological and medical purposes of where it has in vitro anticonvulsant,[3] antiinflammatory,[4] and antihypertensive[5] effects and act as vasopressin antagonists,[6] prompted us to continue the work of our laboratory, which deals with the synthesis of some new 1,5-benodiazepines.[7-9] It has various therapeutic applications, many being used for inducing sleep. Diazepam and nitrazepam are anticonvulsants and flurazepam is both an antianxiety agent and a potent hypnotic.[10,11] The derivatives of 1,5-benzodiazepines are also used as dyes for acrylic fibers in photography[12] In addition, benzodiazepines are the useful precursors for the synthesis of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[13-16] Herein we report the synthesis of some new derivatives of 1,5-benzodiazepines.



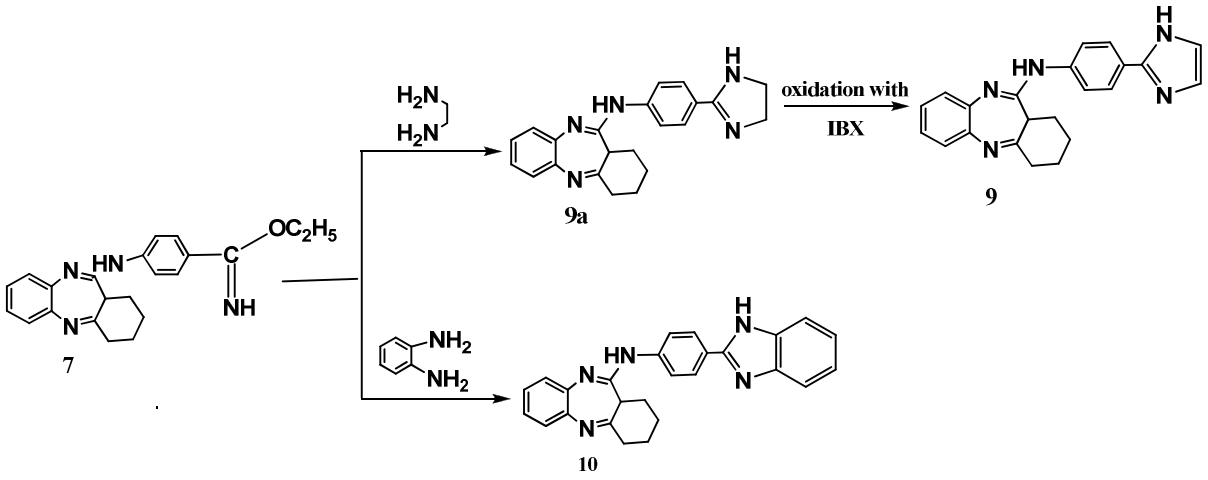
Scheme-1



Scheme-2



Scheme-3



Scheme-4

MATERIALS AND METHODS

Experimental

Melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on Schimadzu FTIR-8400S. ^{1}H-NMR spectra were recorded in $CDCl_3$ on Bruker DRX300 MHz. spectrometer using TMS as internal reference with their values expressed in d ppm. Purity of all the synthesized compounds

were routinely checked through TLC on silica gel G in the solvent system (9:1, benzene: methanol).

Preparation of 2-thiomethyl-cyclohexano-[3,4-c][1,5]-benzodiazepine(2)

A mixture of oxyketenedithio acetal (1) (1.29g, .01mmol) in dmf (20 ml) and o-phenylenediamine (1.08g, 0.01mol), was heated under reflux for 4-5h and then 1 ml of AcOH was added. The refluxing was continued for 1-2h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give (2) (yield: 75%); m.p 130-132^{0}C. IR: 3030 [C-H str. ArH], 1585 [C=C str. ArH], 1520 [C=N str.],1160 [C-N str.],695[C-S str.]; ^{1}HNMR 7.60-8.12[m, 4H, ArH], 7.39[d, 2H, phenoxyl],6.81[d, 2H, phenoxyl],1.29-1.81[m, 4H, cyclohexane] m/z: 244.10 (100.0%), 245.11 (15.3%), 246.10 (4.6%), 245.10 (1.5%), 246.11 (1.2%).

Preparation of 4-(1,2,3,10a-tetrahydrobenzo[b]cyclopentane[e][1,4]diazepin-10-ylamino) benzonitrile(3)

The mixture of (2) (0.23 g, 0.001 mol) and p-amino benzonitrile (0.14g, 0.0012 mol) in DMF (15 ml) potassium-tert-butoxide (0.22 g, 0.002 mol) was slowly added into on ice-water bath, then stirred at room temperature for 6-7 hr until reaction was completed. The mixture was poured into ice water and pH was adjusted to 6 with 5% aqueous HCl and the mixture extracted with EtOAc three times. After removal of organic solvent in vacuo, crude product was purified by TLC or a silica column (eluent: petroleum ether/EtOAc) to give (3) (68% yield); m.p. 165-167°C. IR: 3030 [C-H str. ArH], 1585 [C=C str. ArH], 1520 [C=N str.],1160 [C-N str.],3320 [NH str.], 2210 [CN str]; ^{1}HNMR 1.95 [s, H], 7.33-7.45[m, 4H, ArH], 6.81[d, 2H, phenoxyl], 7.39[d, 2H, phenoxyl],1.28-1.34[m, 4H, cyclohexane],4.0 [s, NH]; m/z: 314.15 (100.0%), 315.16 (21.8%), 316.16 (2.3%), 315.15 (1.5%).

Preparation of 4-(2,3,4,11a-tetrahydro-1H-dibenzo[b,e][1,4]diazepin-1yloxy)benzaldehyde (4)

A mixture of compound (2) (0.23 g., 0.001 mol) 4-hydroxybezonitrile (0.28 g., 0.0012 mol) in DMF (5ml) potassium-tert-butoxide (0.28 g., 0.002 mol) was slowly added into on ice-water bath, then stirred at room temperature for 5 hrs until reaction was completed. Then mixture was poured into ice water and pH was adjusted to 6% with aqueous HCl and the mixture extracted with EtoAc. After removal of the solvent in vacuo, the obtained crude product (4) was purified by PTLC and silica column (eluent: petroleum ether/EtoAc), (0.20 g, yield: 61%); m.p:-230-232 ^{0}C IR: 3030 [C-H str. ArH], 1585 [C=C str. ArH], 1520 [C=N str.],1205 [C-N str.],1095 [C-O str.], 1705 [C=O str.]; ^{1}HNMR; 1.95 [s, CH], 7.33-7.45[m, 4H, ArH], 7.60[d, 2H, phenoxyl], 7.77[d, 2H, phenoxyl], 1.28-1.92[m, 4H, cyclohexane], 2.50 [s, CH_3], m/z: 362.20(100.0%), 363.20 (25.7%), 364.21 (3.1%).

Preparation of 1-(4-(2,3,4,11a-tetrahydro-1H-dibenzo[b,e][1,4]diazepin-11-yloxy)phenyl) ethanone (5)

A mixture of compound (2) (0.23g, 0.001 mol) and P-hydroxy acetophenone(0.16g, 0.0012 mol) in DMF(3ml) potassium-tert-butoxide (0.28 g., 0.002 mol) was slowly added into on ice-water bath, then stirred at room temperature for 5 hrs until reaction was completed. Then mixture was poured into ice water and pH was adjusted to 6% with aqueous HCl and the mixture extracted with EtoAc. After removal of the solvent in vacuo, the obtained crude product (5) was purified by PTLC and silica column (eluent: petroleum ether/EtoAc), (0.90 g, yield: 68%); m.p:-245-247 ^{0}C.

Preparation of N'-hydroxy-4-(2,3,4,11a-tetrahydro-1H-dibenzo[b,e][1,4]diazepin-11-ylami- no)benzimidamide (6)

A solution of 11-(4'-cyanophenylamino)-pyrrolo[2,1-c][1,4]-benzodiazepine-5-one (6) (1.27 g., 0.004 mol) in 30 ml ethanol was added in mixture of hydroxylamine hydrochloride (0.59 g., 0.00857 mol) in water (3

ml) and sodium carbonate (0.69 g., 0.00648 mol) in water (6ml), successively, in the presence of 8- hydroxyquinoline (0.002 g. 0.013 mol), the mixture was heated to reflux for 4 h. monitored by TLC (petroleum ether/EtOAc 1:1:0.03). After removal of ethanol solvent under reduced pressure, the residue was diluted with 30 ml water, and the water solution was slowly acidified with 10% HCl to pH 3.2. The white precipitate was filtrated, washed with water, and dried to give (6) (1.11.g., yield: 79%); m.p: 222-224^{0}C IR: 3030 [C-H str. ArH], 1585 [C=C str. ArH], 1520 [C=N str.], 1160 [C-N str.], 3400 [NH str.], 1665[C=N], 3600[OH], 1665[C-NH]; ^{1}HNMR: 1.95 [s, H], 7.33-7.45[m, 4H, ArH], 1.28-1.92[m, 4H, cyclohexane], 6.50-7.58[m, 4H, ArH], 4.0 [s, NH], 2.0 [s, OH], 7.12[s, NH_2];

Preparation of ethyl 4-(2,3,4,11a-tetrahydro-1H-dibenzo[b,e][1,4]diazepin-11-ylamino) benzimidate (7)

The HCl gas passed for 1 hr through a solution of 11-(4'-cyanophenylamino)-pyrrolo[2,1-c] [1,4] -benzodiazepin-5-one (0.32 g., 0.001 mol) in absolute ethanol and ether was added to the above mixture.. The precipitate was filtered and dried to give **7** (0.23 g., yield: 63%); m.p: 265-267^{0}C.

IR: 3030 [C-H str. ArH], 1585 [C=C str. ArH], 1520 [C=N str.], 1160 [C-N str.], 3400 [NH str.], 1665[C=NH], 1095[C-O str.], ^{1}HNMR: 1.95 [s, H], 7.33-7.45[m, 4H, ArH], 1.28-1.92[m, 4H, cyclohexane], 4.0 [s, NH], 4.0 [s, NH], 7.48-7.09[m, 4H, ArH], 3.58 [s, CH_2], 1.10 [s, C_2H_5], m/z: 360.20 (100.0%), 361.20 (24.1%), 362.20 (3.3%), 361.19 (1.5%).

Preparation of N-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-2,3,4,11a-tetrahydro-1dibenzo [b,e] [1,4]diazepin-11-amine 2.60 (8)

A mixture of (6) (0.35 g., 0.001 mol) and acetyl chloride (0.5 ml) in 1,2-dichlorobenzene (3 ml) was irradiated under microwave at 180^{0}C for 10 min in the presence of dimetylaminopyrimidine (DMAP) (0.1 ml). The mixture was poured into ice-water and pH adjusted to basic with $NaHCO_3$ solution, and the mixture extracted with dichloromethane three times to give (8) (0.25 g., yield: 66%); m.p-235-237^{0}C. IR: 3030 [C-H str. ArH], 1585 [C=C str. ArH], 1520 [C=N str.], 1565 [C=N-O str.], 3400 [NH str.], 1160 [C-N str.]; ^{1}HNMR: 7.33-7.45[m, 4H, ArH], 6.69[d, 2H, phenylamino], 7.90[d, 2H, phenylamino], 1.28-1.95[m, 4H, cyclohexane], 4.0 [s, 1H, NH], 2.62[S, 3H, CH_3]; m/z: 371.17 (100.0%), 372.18 (24.1%), 373.18 (3.4%), 372.17 (1.8%).

Preparation of N-(4-(1H-imidazol-2-yl)phenyl)-2,3,4,11a-tetrahydro-1H-dibenzo[b,e][1,4] di azepin-11-amine (9)

A mixture of (7) (0.43 g., 0.0012 mol) and ethanol (20 ml) was refluxed for 4-5h. The solvent was distilled under reduced pressure and the residue was quenched in ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give 9a. 2-iodoxybenzoic acid (0.56 g., 0.0020 mol) was added all at once to a solution of the obtained residue 9a (1.04 g., 0.0029 mol) in deionized water (6.5 ml, 0.0045 M) in a 100 mL flask. The reaction mixture was warmed to 70-75^{0}C over 20 min and magnetically stirred at this temperature for 3 hrs. The nature of the mixture varied consistently during the reaction. The initial thick slurry coating on the walls of the flask eventually becomes a finely dispersed, easy to be stirred suspension of solid that sediment easily upon stopping the stirring. The suspension was the cooled at 5^{0}C and left at this temperature for 1.5h with slow stirring. The mixture was filtered through a medium porosity sintered-glass funnel, and the solid was repeatedly rinsed with water and acetone to give (9) (0.32 g., yield: 74%); m.p-210-212^{0}C. IR: 3030 [C-H str. ArH], 1585 [C=C str. ArH], 1520 [C=N str.], 3400 [NH str.], 1160 [C-N str.]; ^{1}HNMR: 4.0 [s, 1H, NH], 13.0[s, 1H, NH], 7.33-7.45[m, 4H, ArH], 6.69[d, 2H, phenylamino], 7.90[d, 2H, phenylamino], 1.28-1.95[m, 4H, cyclohexane],7.02 [d, 2H, CH=CH of imidazole]; m/z: 355.18 (100.0%), 356.18 (25.6%), 357.19 (2.8%).

Preparation of N-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-2,3,4,11a-tetrahydro-1H-dibenzo [b,e]- [1,4]diazepin-11-amine (10)

A mixture of o-phenylenediamine (1.08 g., 0.01 mol) and **(2)** (0.44 g., 0.0012 mol) in ethanol (20 ml) was refluxed for 4-5h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate to give (10) (0.37 g., yield: 75%); m.p-198-200^{0}C. IR: 3030 [C-H str. ArH], 1585 [C=C str. ArH], 1520 [C=N str.], 3400 [NH str.], 1160 [C-N str.] ^{1}HNMR: 4.0 [s, 1H, NH], 5.0 [s, 1H, NH], 7.33-7.45[m, 4H, ArH], 6.69[d, 2H, phenylamino], 7.90[d, 2H, phenylamino], 1.28-1.95[m, 4H, cyclohexane],7.22-7.59[m, 4H, ArH]; m/z: 405.20 (100.0%), 406.20 (28.4%), 407.20 (4.4%), 406.19 (1.8%).

Table-1
Physical and analytical data of the compounds (2-8)

S.No	Comp. No	Molecular Formula	M.W.	Yield (%)	M.P.(°C)	Elemental Analysis (Cal / Exp.)			
						C	H	N	S
1.	2	$C_{14}H_{16}N_2S$	244.36	65	130-132°C	68.81/69.15	6.60/6.56	11.46/11.51	13.12/12.88
2.	3	$C_{20}H_{18}N_4$	314.38	50	165-167°C	76.41/76.02	5.77/5.79	17.82/17.73	-
3.	4	$C_{20}H_{18}N_2O_2$	318.14	65	230-232°C	75.45/75.82	5.70/5.72	8.80/7.92	-
4.	5	$C_{21}H_{20}N_2O_2$	332.40	70	245-247°C	75.88/75.50	6.06/6.09	8.43/7.88	-
5.	6	$C_{20}H_{21}N_5O$	347.41	65	222-224°C	69.14/69.48	6.09/6.05	20.16/20.15	-
6.	7	$C_{22}H_{24}N_4O$	360.45	62	265-267°C	73.31/72.94	6.71/6.67	15.54/15.61	-
7.	8	$C_{22}H_{21}N_5O$	371.44	66	235-237°C	71.44/71.79	5.70/5.72	18.85/18.75	-
8.	9	$C_{22}H_{21}N_5$	355.44	74	210-212°C	74.34/74.71	5.96/5.98	19.70/19.60	-
9.	10	$C_{26}H_{23}N_5$	405.49	75	198-200°C	77.01/115.5	5.72/5.74	17.27/17.35	-

RESULTS AND DISCUSSION

Keeping the potential biological activity in mind, it was plan to synthesize benzodiazepine nucleoside by condensation of o-phenylenediamine with oxoketenedithioacetals. In this paper we have synthesized derivatives of face 'C' annulated 1,5-benzodiazepine (2-10). All the synthesized compounds gave satisfactory results of C, N and S analysis, IR, ^{1}H-NMR and Mass Spectral data were found to be consistent to the assigned structures. The physical and analytical Data of the compounds are presented in Table-1.

CONCLUSION

We have synthesized various derivative of face 'C' annulated 1,5-diazepines with good yields. The main advantage of this method is that reactions were found clean and had operational simplicity. In conclusion, several derivatives of face 'C' annulated 1,5-benzodiazepine (2-10) displaying potential antibacterial and antifungal activities were synthesized from the commercially available cylohexanone, o-phenyldiamine by the condensation reaction.

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