A novel one pot, solvent-free Mannich synthesis of methylpiperidinyl phenols, methylphenylmorpholinyl phenols and methylthiophenylmorpholinyl phenols using infrared light irradiation

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Abstract

A series of methylpiperidinyl phenols, methylphenylmorpholinyl phenols and methylthiophenylmorpholinyl phenols were synthesized in one-pot transformation by Mannich reactions using infrared irradiation under solvent-free conditions. The chemical structures of the compounds were proved by IR, ^{1}H NMR, ^{13}C NMR and MS spectroscopic data.

Keywords: Methylpiperidinyl phenols, methylphenylmorpholinyl phenols and methylthiophenyl morpholinyl phenols, one-pot reaction, Mannich, infrared irradiation

Introduction

The Mannich reaction provides an excellent method for carbon-carbon bond formation and its importance is reflected in the ever-increasing number of suitable substrates and reaction conditions that have been developed[1-4]. Some important experimental modifications involve the use of preformed iminium salts[5-9], which can be prepared by a number of methods including the reactions of acetyl chloride with aminals[10], of trifluoroacetic anhydride with N-oxides[11], and of trichloromethylsilane with aminol ethers[12].

This reaction is also one of the most important and fundamental reactions in organic chemistry. It is a powerful tool in routes for the synthesis of various β-amino ketones or esters, which are versatile synthetic building blocks for the preparation of many nitrogen-containing, biologically important compounds[13-17]. In the bimolecular version of the classical Mannich reaction the use of preformed or in situ generated iminium[18] or *N*-acyliminium ions[19-20] and carbon nucleophiles has greatly expanded the versatility of this methodology, allowing the use of

milder reaction conditions. Recently, some significant progress has been made by the use of a number of Lewis acid or transition metal catalyzed Mannich reactions of (1-methoxy-2-methylpropenyloxy) trimethylsilane with imines in organic solvents. For example, the application of zirconium [$Zr(OPr^i)_4$], palladium complexes, and rare earth metal triflates [$Ln(OTf)_n$, Ln=Yb, Sc, Y, La] in the Mannich reaction has enlarged its utility in organic synthesis**.** Further, one-pot transformations, particularly multi-component reactions (MCR)[21-26], are of current interest to organic chemists. Since the first MCR reported in 1850 by Strecker[27], this methodology has emerged as an efficient and powerful tool in modern synthetic organic chemistry, allowing the easy creation of several new bonds in a one-pot transformation. Very recently, transition metal catalyzed MCR reactions of aldehydes, ketones and amines (Mannich reactions) were reported[28]. On the other hand, the reaction of phenols and their derivatives with amines in the Mannich synthesis has been reported using different conditions and using different catalysts. The most common solvents using in this reaction are alcohols such as methanol and ethanol, but benzene and aprotic solvents are also used[29-34]. Methylphenylmorpholinyl phenol derivatives have been used as ligands in zinc complexes[35], and some of them show gastrokinetic activity[36], as antiviral agents[37], as antimalaria agents[38] as spermicides[39] and also as antiarrhythmic agents[40]. Some piperidine derivatives have been used in the treatment of heart disease, as a remedy for auricular fibrillation[41], and as insect repellents[42].

So, we report herein, an efficient and fast method for preparing methylpiperidinyl phenols, methylphenylmorpholinyl phenols and methylthiophenylmorpholinyl phenols, using organic solvent-free Mannich reactions under infrared irradiation. This organic, solvent-free approach requires only a few minutes of reaction time, in contrast to conventional methods that require long reaction times, large excesses of organic solvent and expensive metal catalysts, which can be difficult to handle. To establish the generality of the method, phenols and their derivatives were reacted with formaldehyde and the corresponding amino group, as in piperidine, morpholine or thiomorpholine, in the presence of infrared light produced by a medicinal infrared lamp (250W), to yield the corresponding products.

Results and Discussion

The reactions were accelerated by infrared light and the desired products were obtained in only a few minutes with optimum yields (see Table 1). Infrared light activation as a non-conventional energy source has become an important method that can be used to carry out a wide range of reactions with short reaction times and high yields. Indeed, infrared light heating rapidly increases temperature in absence of the solvent and leads to a uniform energy transfer to the reactants of the chemical reaction. In table 1 we have compared the reaction time and the yield with those reported in the literature. This method does not involve toxic materials, resulting in an economic process, which has clear advantages as an environmentally friendly, solvent-free alternative in organic synthesis. In our experience and, according to the reports in the literature,

when the reaction mixtures were refluxed using ethanol as solvent in the absence of infrared light irradiation, the reaction times were in the range of 1–100 hours and the yields were lower.

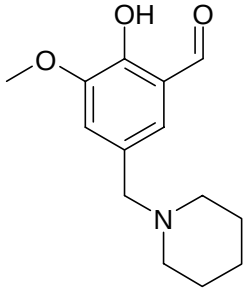
Conclusions

We have reported an efficient and improved three-component coupling reaction for the Mannich synthesis of methylpiperidinyl phenols, methylphenylmorpholinyl phenols and methylthiophenylmorpholinyl phenols, under controlled infrared light irradiation. The method offers several advantages such as it can be performed in a short time, with high yields and without the use of any metal catalyst or solvents

Experimental Section

General procedures. An appropriate phenol (1 eq.), formaldehyde (2 or 4 eq.) and piperidine or morpholine or thiomorpholine (1 or 2 eq.) were mixed in a round flask fitted with a condenser. The mixture was irradiated with infrared light using a medicinal infrared lamp (250 Watts) and the reaction was monitored by tlc. The mixture was chromatographed on silica gel using a solvent gradient hexane/ethyl acetate. Some products were known and their physical data were compared with those of the authentic samples and their spectroscopic signals reported. The reaction temperature is in the range of 120°C to 180°C. The results are shown in Table 1.

2-Hydroxy-3-methoxy-5-(piperidin-1-ylmethyl)benzaldehyde. Mp 121-122 °C, yield 82%. Reaction time: 25 minutes

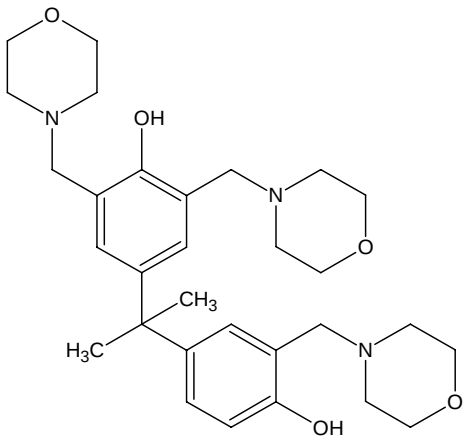


IR (cm^{-1}; $CHCl_3$ film) 3520, 3158, 2932, 1650. ^{1}H-NMR (200 MHz; $CDCl_3$; Me_4Si, δ_H): 10.12 (1H, s, OH), 9.76(1H), 7.33 (1H, d, J=1.8Hz), 7.14 (1H, d, J=1.8Hz), 3.93 (3H,s), 3.78 (2H, s), 2.58 (4H, m), 1.67 (4H,m). ^{13}C-NMR (δ_C): 190.65, 154.80, 148.81, 127.82, 125.40, 120.85, 109.55, 61.45, 55.93, 53.69, 25.62, 23.69. FAB-MS (M+1) 250. Calculated for $C_{14}H_{19}NO_3$, C 67.45%, H 7.68%, N 5.62%, O19.25%.

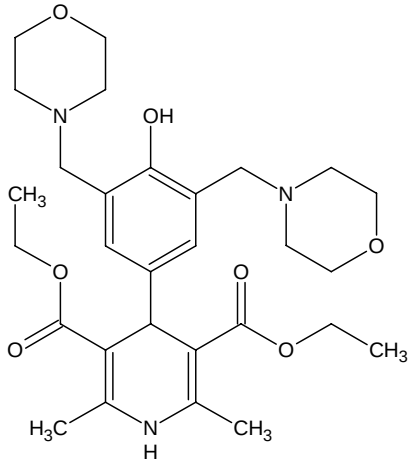
4-[1-(4-Hydroxy-3-morpholin-4-ylmethylphenyl)-1-methylethyl]-2,6-bis(morpholin-4-ylmethyl)phenol. Mp 248-250 °C, yield 50%. Reaction time: 17 minutes.

IR (cm^{-1}; $CHCl_3$ film) 3575, 3158, 2932. ^{1}H-NMR (300 MHz; $CDCl_3$; Me_4Si, δ_H): 8.59 (2H, s, OH), 6.98 (1H, dd, 8.4Hz, 2.4Hz), 6.88 (1H, s), 6.81 (1H,d,2.4Hz), 6.69 (1H,d, 8.4Hz), 3.72 (12H, m), , 3.64 (2H, s, Ar-CH_2), 3.60, (4H, s, Ar-CH_2), 2.51 (12H,m), 1.586 (6H,s). ^{13}C-NMR

(δ_C): 154.95; 153.67; 141.75; 141.06; 127.58; 127.18; 126.76; 120.76; 119.61; 115.21; 66.65, 62.04; 59.33; 52.91; 41.35; 31.03. FAB-MS (M+1) 526 (25%), 439 (100%), 352 (80%). Calculated for $C_{30}H_{43}N_3O_5$, C 68.54%; H 8.24%; N 7.99%; O 15.22%.

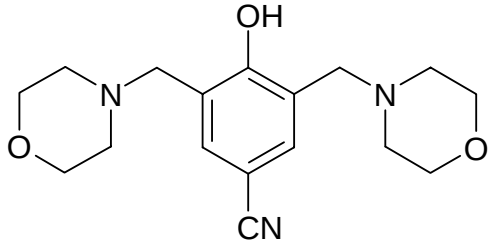


4-(4-Hydroxy-3,5-bis(morpholin-4-ylmethylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester. Mp 145 – 147 °C. Yield, 85%. Reaction time: 10 minutes.



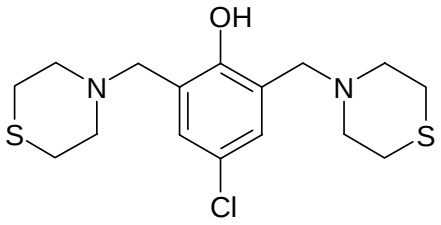
IR (cm^{-1}; $CHCl_3$ film) 3450, 3540, 3056, 2932, 1691. ^{1}H-NMR (300 MHz; $CDCl_3$; Me_4Si, δ_H): falta (1H, s, OH), 6.93 (2H, s), 5.58 (s, 1H), 4.87 (s, 1H), 4.1 (4H,q,), 3.71 (8H, m), 3.51 (2H, s), 2.49, (8H, m), 2.35 (6H, s)1.22 (6H, t). ^{13}C-NMR (δ_C): 167.7; 154.2; 143.3; 138.2; 128.7; 121.1; 104.4; 66.9; 59.5; 53.2; 38.7; 19.6; 14.3. FAB-MS (M+1) 544 (20%), 456 (96%), 252 (100%). Calculated for $C_{29}H_{41}N_3O_7$, C 64.07%; H 7.60%; N 7.73%; O 20.60%.

4-Hydroxy-3,5-bis(morpholin-4-ylmethyl)benzonitrile. Mp 104 - 106°C. Yield 87%. Reaction time: 15 minutes



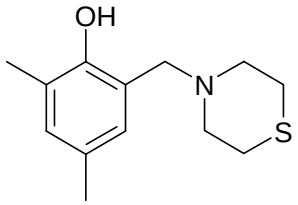
IR (cm^{-1}; $CHCl_3$ film) 3455, 3056, 2932, 2230. ^{1}H-NMR (300 MHz; $CDCl_3$; Me_4Si, δ_H): 11.4 (1H, s, OH), 7.14 (2H, s), 3.72 (8H, m), 3.63 (2H, s), 2.54, (8H, m). ^{13}C-NMR (δ_C): 162.2; 132.48; 123.48; 119.34; 101.75; 66.56; 58.34; 53.03. FAB-MS (M+1) 318 (34%), 230 (100%), 229 (45%). Calculated for $C_{17}H_{23}N_3O_3$; C 64.33%; H 7.30%; N 13.24%; O 15.12%.

4-Chloro-2,6-bis(thiomorpholin-4-ylmethyl)phenol. M.p. 118-120, Yield 78%, Reaction time: 12 minutes.



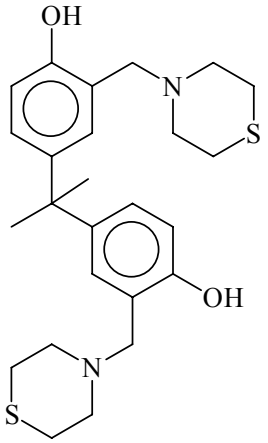
IR (cm^{-1}; $CHCl_3$ film) 3554, 3034, 2932. ^{1}H-NMR (200 MHz; $CDCl_3$; Me_4Si, δ_H): 10.93 (1H, s, OH), 7.03 (2H, s), 3.59 (4H, s), 2.79 (8H, m), 2.71 (8H, m). ^{13}C-NMR (δ_C): 154.70, 128.31, 124.12, 123.46, 59.14, 54.60, 27.84. FAB-MS (M+1)359 (25%**).** Calculated for $C_{16}H_{23}ClN_2OS_2$; C 53.54%, H 6.46%, Cl 9.88%, N 7.80%, O 4.46%, S 17.87%

2,4-Dimethyl-6-(thiomorpholin-4-ylmethyl)phenol. M.p. 93-95, Yield 85%, Reaction time: 4 minutes.



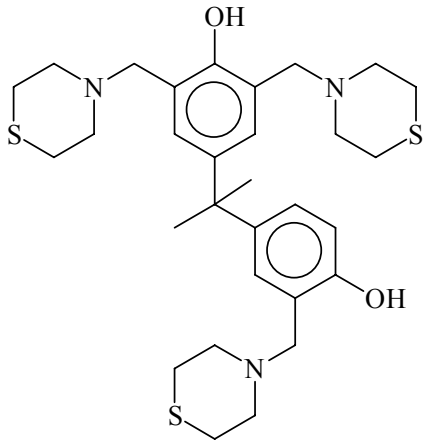
IR (cm^{-1}; $CHCl_3$ film) 3502, 3034, 2932. ^{1}H-NMR (200 MHz; $CDCl_3$; Me_4Si, δ_H): 10.47 (1H, s, OH), 6.85 (1H, s), 6.61 (1H,s), 3.62 (2H, s), 2.78 (4H, m), 2.18 (4H, m), 2.12 (3H,s), 2.10 (3H,s). ^{13}C-NMR (δ_C): 153.28, 130.64, 127.76, 126.79, 124.64, 119.76, 62.33, 54.36, 27.90, 20.35, 15.53. FAB-MS (M+1) 238 (15%). Calculated for $C_{13}H_{19}NOS$; C 65.78%, H 8.07%, N 5.90%, O 6.74%, S 13.51%.

4-[1-(4-Hydroxy-3-thiomorpholin-4-ylmethylphenyl)-1-methylethyl]-2-(thiomorpholin-4-ylmethyl)phenol. Mp 163-165 °C. Yield 50%. Reaction time: 11 minutes



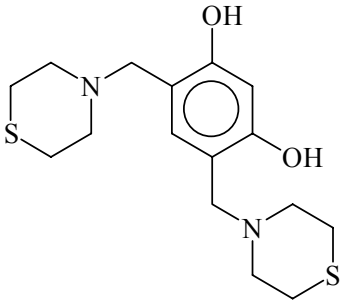
IR (cm^{-1}; $CHCl_3$ film) 3409, 3050, 2956 . ^{1}H-NMR (300 MHz; $CDCl_3$; Me_4Si, δ_H): 10.42 (2H, s, OH), 7.0 (2H, dd, J=1.6Hz, 5.6Hz), 6.79 (2H, d, 1.6Hz), 6.69 (2H, d, 5.6Hz), 3.64 (4H, s), 2.80 (8H, m), 2.71, (8H, m), 1.57 (6H,s). ^{13}C-NMR (δ_C): 155.09; 141.70, 127.06, 126.85, 119.78, 11.30, 62.48, 54.35, 41.38, 31.07, 27.83. FAB-MS (M+1) 459 (100%), 354 (60%), 253 (40%), 102 (80%). Calculated for $C_{25}H_{34}N_2O_2S_2$, C 65.46%; H 7.47%; N 6.11%; O 6.98%; S 13.98%.

4-[1-(4-Hydroxy-3-thiomorpholin-4-ylmethylphenyl)-1-methylethyl]-2,6-bis(thiomorpholin-4-ylmethyl)phenol. M.p. 136-138 °C. Yield 45%. Reaction time: 15minutes



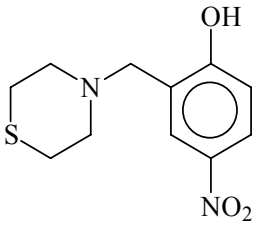
IR (cm^{-1}; $CHCl_3$ film) 3476, 3035, 2906. ^{1}H-NMR (200 MHz; $CDCl_3$; Me_4Si, δ_H): 10.22 (2H, s, OH), 6.97 (1H, dd, J=2.4Hz, 8.4Hz), 6.84 (1H, s), 6.80 (1H, d, J=8.4Hz), 6.69 (1H, d, J=2.4Hz), 3.62 (2H, s), 3.58 (4H, s), 2.74 (12H, m), 2.65, (12H, m), 1.58 (6H,s). ^{13}C-NMR (δ_C): 155.19, 153.76, 141.88, 141.07, 127.28, 126.82, 121.34, 119.79, 115.40, 62.66, 59,87, 54.48, 41.44, 31.14, 27,87. FAB-MS (M+1) 574 (50%), 471 (100%), 368(50%), 116(60%), 102 (50%). Calculated for $C_{30}H_{43}N_3O_2S_3$, C 62.79%; H 7.55%; N 7.32%; O 5.58%; S 16.76%.

4,6-Bis(thiomorpholin-4-ylmethyl)benzene-1,3-diol. M.p. 193-195 °C. Yield 87%. Reaction time: 11 minutes



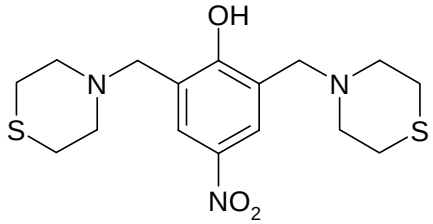
IR (cm^{-1}; $CHCl_3$ film) 3485, 3034, 2980. ^{1}H-NMR (300 MHz; $CDCl_3$; Me_4Si, δ_H): 10.11 (2H, s, OH), 6.54 (1H, s), 6.31 (1H, s), 3.59 (4H, s), 2.80 (8H, m), 2.71, (8H, m). ^{13}C-NMR (δ_C): 158.3; 128.73, 11.49, 103.89, 61.59, 54.23, 27.82. FAB-MS (M+1) 341 (25%), 340 (37%), 238 (100%), 154(85%), 136 (62%). Calculated for $C_{16}H_{24}N_2O_2S_2$, C 56.44%; H 7.10%; N 8.23%; O 9.40%; S 18.83%.

4-Nitro-2-(thiomorpholin-4-ylmethyl)phenol. M.p.193-195 °C. Yield 30%. Reaction time: 16 minutes.



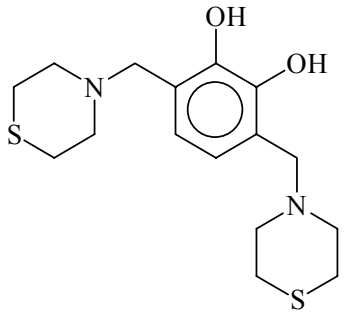
IR (cm^{-1}; $CHCl_3$ film) 3498, 3030, 2987. ^{1}H-NMR (300 MHz; $CDCl_3$; Me_4Si, δ_H): 10.44 (1H, s, OH), 8.12 (1H, dd, J=1.8Hz, 6Hz), 7.95 (1H, d, 1.8Hz), 6.85 (1H, d, 6Hz), 3.81 (2H,s), 2.87 (4H,m), 2.76 (4H,m). ^{13}C-NMR (δ_C): 164.12, 140.14, 125.33, 124.80, 120.72, 116.48, 61.49, 54.27, 27.65. FAB-MS (M+1) 257 (10%), 255 (100%), 254 (55%), 154 (30%). Calculated for $C_{11}H_{16}N_2O_3S$. C 51.54%; H 6.29%; N 10.93%;O 18.73%; S 12.51%.

4-Nitro-2,6-bis(thiomorpholin-4-ylmethyl)phenol. M.p. 151-152 °C. Yield 90%. Reaction time: 10 minutes.



IR (cm^{-1}; $CHCl_3$ film) 3490, 3026, 2970. ^{1}H-NMR (200 MHz; $CDCl_3$; Me_4Si, δ_H): 10.56 (1H, s, OH), 8.01 (2H, s), 3.69 (4H,s), 2.82 (8H,m), 2.72 (8H,m). ^{13}C-NMR (δ_C): 162.52, 139.85, 124.58, 123.12, 58.93, 54.60, 27.78. FAB-MS (M+1) 372 (10%). Calculated for $C_{16}H_{25}N_3O_3S_2$. C 51.73%, H 6.78%, N 11.31%, O 12.92%, S 17.26%.

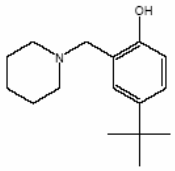
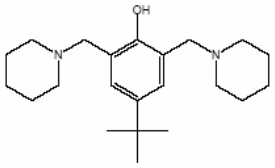
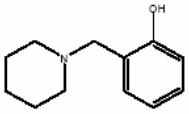
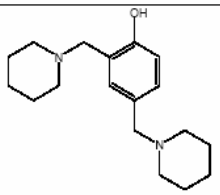
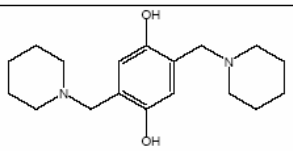
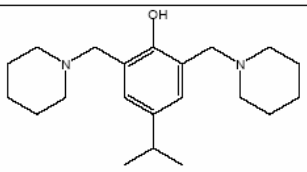
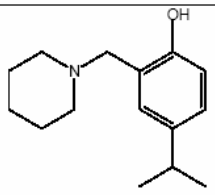
3,6-Bis(thiomorpholin-4-ylmethyl)benzene-1,2-diol. M.p.236-238 °C. Yield 63%. Reaction time: 14 minutes.

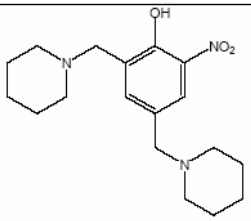
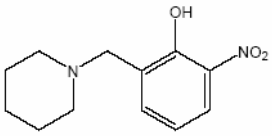
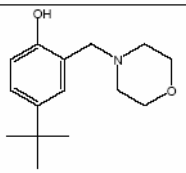
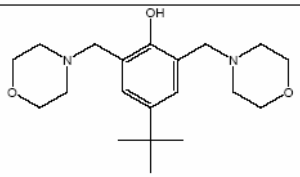
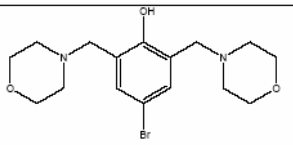
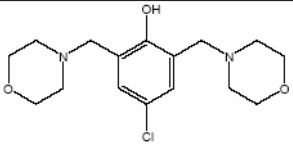
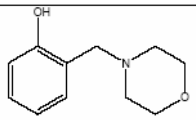
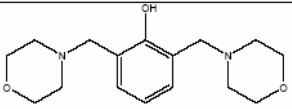
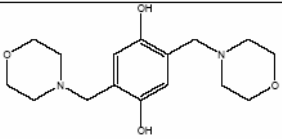


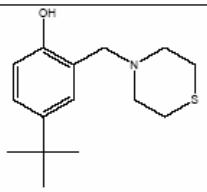
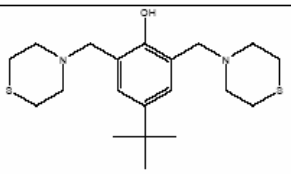
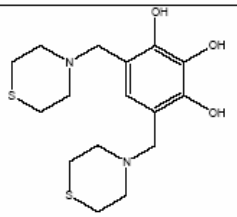
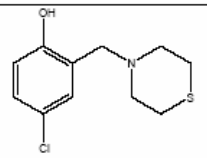
^{1}H-NMR (200 MHz; $CDCl_3$; Me_4Si, δ_H): 8.55 (2H, s, OH), 6.42 (2H, s), 3.68 (4H, s), 2.83 (8H, m), 2.72, (8H, m). ^{13}C-NMR (δ_C): 145.58, 120.82, 118.73, 62.08, 54.42, 27.93.

FAB-MS (M+1) 341 (10%), 307(30%), 154 (100%), 136(65%). Calculated for $C_{16}H_{24}N_2O_2S_2$. C 56.44%; H 7.10%; N 8.23%; O 9.40%; S 18.83%.

Table 1. Comparative results of reaction of phenols+amine+formaldehyde

Phenol	Amine	Product	m.p.; b.p.* °C Lit.	m.p.Exp.	Time lit. hrs	Time (IR) hrs	Yield % lit.	Yield % (IR)	Ref
p-terbutyl-phenol	Piperidine		48.5-49.5	47-48	NA	0.4	NA	70	43
p-terbutyl-phenol	Piperidine		120	119-121	24	0.4	NA	54	44
Phenol	Piperidine		100 *	NA	41	0.3	51	75	45
Phenol	Piperidine		150*	NA	43	0.3	10	80	45
Hydro-quinone	Piperidine		196-198	195-197	6	0.4	69	75	46
p-Isopropyl-phenol	Piperidine		Oil NA	NA	5	0.35	NA	54	47
p-Isopropyl-phenol	Piperidine		Oil NA	NA	6	0.3	54	70	48

2-Nitrophenol	Piperidine		112-114	111-113	22	0.35	NA	70	49-50
2-Nitrophenol	Piperidine		NA(oil)	NA	10	0.33	54	60	51-55
p-Terbutyl-phenol	Morpholine		80-82	75-78	NA	0.4	NA	58	43
p-Terbutyl-phenol	Morpholine		128-130	129-131	5	0.4	82	80	43
p-Bromophenol	Morpholine		115-115.5	114-116	6	0.2	82	92	56
p-Chlorophenol	Morpholine		NA	114-116	NA	0.15	NA	85	57
Phenol	Morpholine		95-96	95-97	96	0.15	NA	90	58
Phenol	Morpholine		123-124	119-121	15	0.15	20	95	56
Hydro-quinone	Morpholine		201-203	202-204 desc.	8	0.15	NA	90	59

p-Terbutyl-phenol	Thio-morpholine		85-87	85-87	48	0.15	5	70	60
p-Terbutylphenol	Thio-morpholine		95-97	95-97	48	0.25	35	80	60
Pyrogalol	Thio-morpholine		181-183	181-183	0.1	0.01	83	85	61
p-Chlorophenol	Thio-morpholine		127-129	127-129	240	0.11	25	60	62

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