

Fe(HSO₄)₃ as an Efficient Catalyst for Diazotization and Diazo Coupling Reactions

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ABSTRACT. Diazo coupling reactions of aromatic amines with 2-naphthol in a green, efficient and easy procedure is described. Ferric hydrogensulfate catalyses this reaction in water at room temperature and short reaction time with high yields. The antibacterial activities of the synthesized compounds against four pathogenic bacteria are also investigated.

Key words: Diazotization, Fe(HSO₄)₃, 2-Naphthol

INTRODUCTION

Diazo coupling reactions is one of the most important class of organic reactions which is currently performed with mineral acids as catalysts.^{1,2} Azo dyes are generally synthesized in two steps: the diazotization of aromatic primary amines followed by the coupling reaction between diazonium salts and phenols or aromatic amines.³ The formation of diazotizing reagent starts with protonation of nitrous acid under strongly acidic conditions and azo coupling carried out at low temperature in the presence of nucleophilic coupling components. The reactivity of a nucleophilic substrate increases with increasing basicity of phenolates and amines.^{4,5} The main limitation of such synthetic processes is their environmental incompatibility. The acidic and basic effluents from the laboratory and industry cause permanent damage to the environment and disturb the ecological balance.^{6,7}

Many azo compounds, besides their uses as dyes, showed antibacterial and antifungal activities.⁸⁻¹⁰ Recently, a series of diaryl-azo derivatives were synthesized and introduced as potent antifungal agents.¹¹

In recent years, much attention has been directed toward the application of solid acids in organic synthesis.¹² Herein, we report a novel simple synthetic method for azo dyes in water as solvent at room temperature in the presence of ferric hydrogensulfate (FHS) as catalyst. We applied green chemistry to the synthesis of azo dyes and found that the reaction occurred in a very short time with high yields.

FHS is low-cost, widely available and is largely used in a variety of lewis acid-catalyzed reactions.¹³⁻¹⁹

EXPERIMENTAL SECTION

General Procedure

To a stirred mixture of NaNO₂ (2 mmol, 0.14 g) and silica gel (1 g), a suspension of an appropriate aromatic amine (2 mmol) and FHS (10 mol%, 0.03 g) in water (5 ml) was added. After the mixture was stirred a bit of time, 2-naphthol (2 mmol, 0.29 g) was added. The progress of the reaction was monitored by TLC using chloroform: methanol as eluent (9:1). After the completion of the reaction, the mixture was filtered and the residue was washed with hot water. The solid was heated in ethanol, filtered and the filtrate was recrystallized in ethanol.

1-(2-(4-Ethylphenyl)diazenyl)naphthalen-2-ol: (Table 1, entry 6): Yield = 91%; m.p. = 121–123 °C; ¹H NMR (CDCl₃, 100 MHz, δ /ppm) 1.41 (t, 3H, –CH₃, *J* = 8.5 Hz), 2.54 (q, 2H, –CH₂, *J* = 8.5 Hz), 6.85 (d, 2H, aromatic, *J* = 7.5 Hz), 7.22 (d, 2H, aromatic, *J* = 7.5 Hz), 7.31–7.83 (m, 5H, aromatic), 8.61 (d, 1H, aromatic, *J* = 7.5 Hz), 16.12 (br s, 1H, –OH, D₂O exchangeable); IR (KBr disc, cm^{–1}) 3300 (OH stretching), 3050 (C–H stretching of aromatic ring), 2958 (C–H stretching of aliphatic ring), 1508 (N=N stretching).

Antibacterial Assay

Microbial strains: *Staphylococcus aureus* (PTCC 1431), *Bacillus cereus* (PTCC 1247), *Pseudomonas aeruginosa*

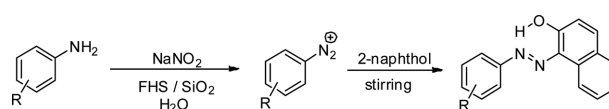
(PTCC 1047), and *Escherichia coli* (PTCC 1399) were recovered from long-term storage at 85 °C in 15% glycerol. Bacteria were refreshed in Trypticase Soy Broth (Merck, Darmstadt, Germany) at 37 °C and inoculated on Trypticase Soy (Merck, Darmstadt, Germany) plates in order to check their purity.

Determination of minimum inhibitory concentration (MIC): The in vitro antibacterial activity of the synthesized diazo compounds were determined using the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) recommended MIC protocol with modifications.^{25,26} Sterile 96-well microplates were used for the assay (0.34 ml volume, Orange Scientific). Bacterial strains were cultured overnight at 37 °C in Muller Hinton Broth (MHB, Oxoid). Stock solutions of the compounds and standard (chloramphenicol) were prepared in 5.0% (v/v) DMSO. Dilution series, using MHB, were prepared from 5 mg/ml to 10 µg/ml. 70 µl of each diluted solution were transferred into 96-well microtitre plates, followed by adding 70 µl of MHB and inoculating 70 µl of the standardized microorganism suspensions containing 10⁸ colony according to McFarland turbidity standards (cfu/ml). A well, consisting of MHB 5.0% (v/v) DMSO and microorganisms, was the growth control and a well, containing MHB, 5.0% (v/v) DMSO and the test oil was the sterility control. The microorganism growth inhibition was evaluated by measuring absorbance at 630 nm by using an ELISA reader (Statfax-2100, Awareness Technology Inc., USA). Chloramphenicol was used as an antibacterial standard against all pathogens. Experiments were performed in triplicate and the averages were reported.

RESULTS AND DISCUSSION

In the present study, a novel method for the nitration of phenol by NaNO₂ and FHS is described. This nitration occurred probably through a nitrosonium ion producing first the nitrosophenol which then oxidized to nitrophenol. In order to prove this proposal, the reaction was performed with *o*-phenylenediamine. As expected the benzo[*d*][1,2,3]triazole was obtained in high yield. Therefore, we supposed that the reagent provide nitrozonium ion intermediate which conduct the diazotization reactions. These observations led us to explore the potential of various substituted anilines to be diazotized and coupled with 2-naphthol under green and mild reaction conditions (*Scheme 1*).

In this work, we have used 2-naphthol as a model aromatic molecule. The study of its behavior can give more



Scheme 1.

reliable information about the reactions of this class of compounds than studies on phenols and other aromatic compounds. Moreover, silica was used as an inert substrate to enhance the water solubility of 2-naphthol to enable a relatively homogeneous mixture.

In order to ascertain the optimum conditions, several reactions were carried out on aniline as the model substrate by varying the amount of the catalyst and finally the best result was obtained with 10 mol% of the catalyst.

Having established the reaction condition, to a mixture of equimolar sodium nitrite and silica gel in a little water, a mixture of various substituted anilines and FHS were added. The mixture was stirred for a few seconds and after that 2-naphthol was added and the mixture was stirred at room temperature. The results of the completion of the reaction were summarized in *Table 1*.

As it can be seen from the data in *Table 1*, variety of aniline derivatives was screened and the corresponding diazo compounds were obtained in good to excellent yields. Aromatic compounds having electron donating group (entries 2,3,6,7) readily underwent diazotization coupling reaction in excellent yields. Also, deactivated aromatic compounds underwent the reaction in good yields (entries 4,5) with a relatively longer time. The steric effect of ortho-substituents in comparing with para-sub-

Table 1. Diazo coupling reaction of aniline derivatives with 2-naphthol in the presence of FHS.

Entry	R	Time (min)	Yield ^a (%)	mp (°C)	mp (°C) ^{Lit.}
1	H	10	90	134–135	133–134 ²⁰
2	4-CH ₃	5	92	133–135	132–134 ²⁰
3	4-CH ₃ O	3	97	136–138	136–137 ²⁰
4	4-F	10	90	143–145	146–148 ²⁰
5	4-Cl	12	86	164–166	165–166 ²⁰
6	4-CH ₃ CH ₂	5	91	121–123	–
7	4-CH ₃ CH ₂ O	3	96	133–134	133–134 ²¹
8	2-CH ₃	10	93	132–133	131–132 ²²
9	3-CH ₃	10	90	140–141	141–142 ²²
10	2-CH ₃ CH ₂ O	12	87	142–143	142–143 ²²
11	2-CH ₃ -3-CH ₃	10	88	130–131	125–130 ²³
12	2-CH ₃ O-5-Cl	15	90	202–204	202–203 ²³
13	4-H ₂ N-C ₆ H ₄	20	80	301–302	300–302 ²⁴

^aisolated yield

Table 2. Minimum inhibitory concentration (MIC = µg/ml) values of the synthesized compounds

Entry	Gram-positive bacteria		Gram-negative bacteria	
	<i>B. cereus</i> PTCC ^a 1247	<i>S. aureus</i> PTCC 1431	<i>E. coli</i> PTCC 1399	<i>P. aeruginosa</i> PTCC 1074
1	> 500	> 500	333	42
2	> 500	> 500	166	333
3	> 500	> 500	> 500	> 500
4	> 500	> 500	166	333
5	> 500	> 500	> 500	100
6	166	166	166	333
7	> 500	> 500	> 500	> 500
8	> 500	> 500	> 500	> 500
9	> 500	> 500	> 500	> 500
10	> 500	333	> 500	> 500
11	> 500	> 500	> 500	> 500
12	333	> 500	166	> 500
Cp. ^b	250	125	62	250

^aPersian Type Culture Collection (PTCC).^bChloramphenicol.

stituents has relatively a bit influence on the reaction time and yields (entries 8, 10–12). It is pertinent to mention that 3-nitro and 4-nitro aniline were rather failed in diazotization coupling reaction. Notably, 2-naphthol underwent smooth and regioselective diazotization reaction with aniline-like derivatives whereas the other aromatic compounds like phenols, toluene, benzonitrile and bromobenzene did not obtain the desired products. The structures of all the synthesized azo compounds were well characterized by ¹H NMR, FT-IR and also melting points were compared with those of the authentic samples in literatures.

The antibacterial activities of the synthesized azo compounds against four pathogenic bacteria (*S. aureus*, *B. cereus*, *P. aeruginosa*, and *E. coli*) were also investigated in vitro using the broth microdilution method according to standard method.^{25,26} Chloramphenicol was used as an antibacterial standard against all pathogens.

As shown in Table 2, the minimum inhibitory concentration (MIC) values of azo compounds were evaluated. Among all screened compounds, entries 1 and 5 exhibited a good antibacterial activity against the *P. aeruginosa* whereas entry 6 showed a good antibacterial activity against *S. aureus* and *B. cereus*. The other synthesized compounds did not show any significant antibacterial activities.

In summary, we have developed a highly efficient green method for the synthesis of azoic dyes catalyzed by eco-friendly catalyst with high yields. This method totally avoids the use of strong protic acids or toxic solvents through the reaction. The resulting diazonium salts react rapidly with 2-naphthol to produce azo dyes in good yields. Our new method has some advantages over traditional

methods which includes mild reaction conditions at room temperature, short reaction time and an easy work-up procedure.

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