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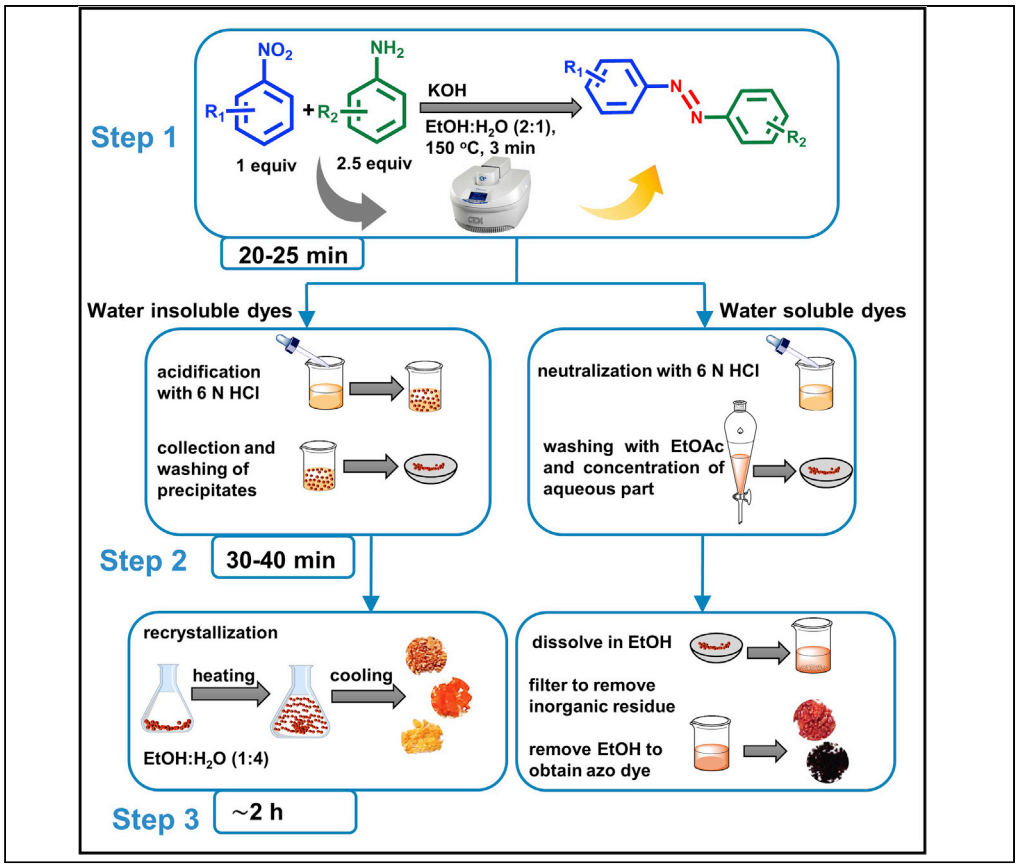
Protocol for microwave-assisted synthesis of unsymmetrical azo dyes



Aromatic azo dyes bear immense commercial significance because of their extensive usage in the textile, paint, and food industries. With growing environmental concerns, developing alternative greener approaches for the synthesis of azo dyes is crucial. Herein, we describe a metal-free, microwave (MW)-assisted protocol for rapid access to a large variety of unsymmetrical azo dyes by coupling nitroarenes and aromatic amines. After MW-assisted coupling, the azo dyes are then isolated by precipitation followed by recrystallization to obtain pure azo dyes.

Publisher's note: Undertaking any experimental protocol requires adherence to local institutional guidelines for laboratory safety and ethics.

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Highlights

Microwave-assisted coupling of nitroarenes and aromatic amines for azo dye synthesis

Metal-catalyst-free, rapid access to a large variety of unsymmetrical azo dyes

Easy isolation and purification process resulting in high percentage yield

Facile generation of dispersed and water-soluble azo dyes including commercial dyes

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Protocol for microwave-assisted synthesis of unsymmetrical azo dyes

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SUMMARY

Aromatic azo dyes bear immense commercial significance because of their extensive usage in the textile, paint, and food industries. With growing environmental concerns, developing alternative greener approaches for the synthesis of azo dyes is crucial. Herein, we describe a metal-free, microwave (MW)-assisted protocol for rapid access to a large variety of unsymmetrical azo dyes by coupling nitroarenes and aromatic amines. After MW-assisted coupling, the azo dyes are then isolated by precipitation followed by recrystallization to obtain pure azo dyes.

For complete details on the use and execution of this protocol, please refer to Thakuri et al. (2022).[1]

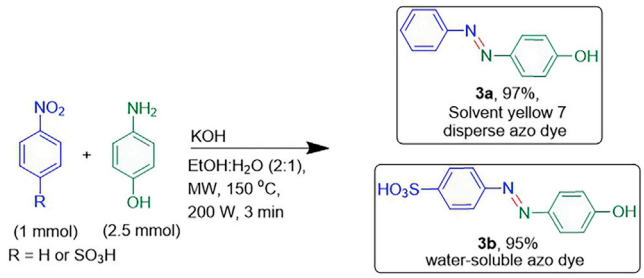
BEFORE YOU BEGIN

Aromatic azo dyes bear intense color and as such exhibit excellent dyeing properties.[2,3] Several classes of azo dyes used in various industries such as textile, paper, and paint account for more than 50% of the worlds commercial dyes.[4–6] Despite being predominantly used as coloring agents azoarenes have found widespread applications as photochemical switches,[7] chemosensors[8] and biomedical agents.[9] With such versatile applications the development of suitable methods for the preparation of azo dyes has garnered significant scientific attraction. Conventionally, the synthesis of azo dyes is carried out via coupling reaction between a diazonium salt and an electron rich aromatic system.[10–13] Several reports for the synthesis of azo dyes utilize catalytic oxidation of aromatic amines[14–16] or reduction of nitroarenes.[17,18] However, in most cases, only symmetrical azo dyes are obtained, whereas, most of the commercial azo dyes bear an unsymmetrical skeleton. Apart from diazotization, coupling between aniline derivatives and aromatic nitroso compounds, commonly known as Mill's reaction, is employed to generate unsymmetrical azo dyes.[19,20] In recent times growing environmental concerns have led to increasing efforts in search of sustainable methods for the preparation of azo dyes. Herein, we describe a metal-catalyst free rapid microwave-assisted synthesis of unsymmetrical azo dyes (Scheme 1).

Reagent preparation

Timing: 10–15 min

1. Prepare 10 M KOH solution.
2. Prepare 6 N HCl solution.



Scheme 1. General route for microwave-assisted synthesis of unsymmetrical aromatic azo dyes

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
4-Aminophenol	Sigma-Aldrich	Cat# 8.00421
4-Chloronitrobenzene	Sigma-Aldrich	Cat# C59122
Nitrobenzene	Sigma-Aldrich	Cat#8.06770
4-Nitrobenzenesulfonate	TCI	Cat# N0140
4-Nitrophenol	Sigma-Aldrich	Cat# 241326
Potassium hydroxide flakes	MolyChem	Cat# 17220
Hydrochloric acid	MolyChem	Cat# 14860
Ethanol	China make	Cat# C59122
Software and algorithms		
ChemDraw Professional 18.0	PerkinElmer	https://www.perkinelmer.com/category/chemdraw
Other		
CEM SP Discover Microwave	CEM	https://cem.com/media/contenttype/media/literature/b087v8-cem.pdf
BUCHI Rotavapor R-100	BUCHI	https://assets.buchi.com/image/upload/v1662999820/pdf/Technical-Datasheet/TDS_11594117_R-100.pdf

MATERIALS AND EQUIPMENT

10 M KOH solution		
Reagent	Final concentration	Amount
KOH	10 N	28 g
DI water	N/A	50 mL
Total	**N/A**	**50 mL**

6 N HCl solution		
Reagent	Final concentration	Amount
HCl	6 N	51.5 mL
DI water	N/A	48.5 mL
Total	**N/A**	**100 mL**

Note: Store all solutions in a fume hood at room temperature (25°C–30°C). The HCl solution can be stored up to 14 days. The NaOH solution should be prepared in small batches and used within 7 days.

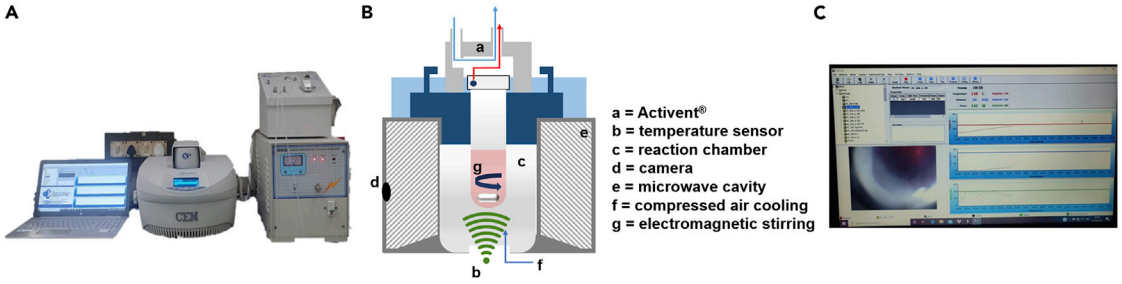


Figure 1. A typical microwave reactor setup
(A) CEM SP Discover microwave system.
(B) Schematic diagram of the internal set-up of microwave reactor.
(C) Image of the microwave method with a video of the reaction method on Synergy.

STEP-BY-STEP METHOD DETAILS

Microwave irradiation: Azo dye synthesis

Timing: 20–25 min

In this major step, the reaction mixture is subjected to microwave irradiation to afford aromatic azo dyes via the coupling of nitroarenes and aromatic amines.

1. Add 1 mmol of nitrobenzene and 2.5 mmol of 4-aminophenol to a 10 mL microwave reaction vial and dissolve the mixture in 2 mL ethanol.
2. To the microwave reaction vial add 1 mL of 10 M KOH and shake for 30 s.
3. Set the vial in a microwave reactor (Figure 1). The microwave method is set to dynamic, with 150°C, 200 W power and 250 psi pressure for 3 min. The reaction displays a color change usually going towards brownish red.
4. After completion of microwave irradiation, allow the microwave reactor to cool and the ActiVent is automatically released (about 5–10 min).
5. Take TLC from the aqueous-ethanolic reaction mixture to confirm the completion of the reaction. (Figure 2).
6. Concentrate the reaction mixture in the rotary evaporator under reduced pressure (40 mbar) to about one-third of its original volume.

⚠ CRITICAL: It is recommended to keep the volume of the solvent to one-third of the volume of the reaction vial (3 mL of the reaction mixture for 10 mL reaction vial). Any increase in volume may lead to rapid pressure build-up and in extreme cases, the vessel may explode.

Isolation of azo dyes

Timing: 30–40 min

In this step, the azo dye is isolated from the reaction mixture. The first step in this process is the acidification of the reaction mixture. Azo dyes can be broadly classified into two categories: (a) Water-insoluble or dispersed azo dyes and (b) water-soluble azo dyes (e.g., azo dyes in the salt form having acidic functionalities like -COOH, -SO_3H). Depending on the solubility isolation of azo dyes follows different steps as mentioned below.

7. Synthesis of water soluble or insoluble dyes.
   a. For water insoluble dyes: Synthesis of (*E*)-4-(Phenyldiazenyl)phenol (3a).
      i. Acidify the reaction mixture is acidified with 6 N HCl (~1.5 mL) to pH 3–4.

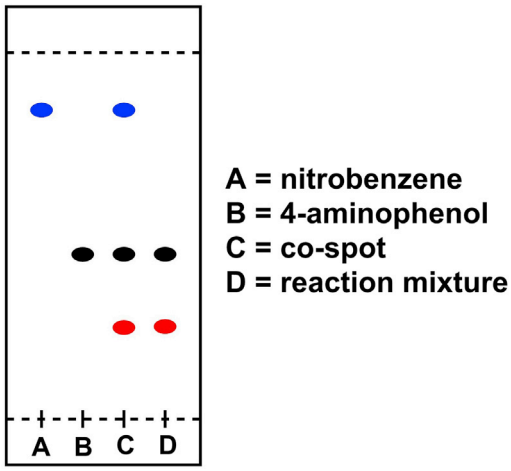


Figure 2. A representative TLC trace of the formation of solvent yellow 7, 3a (R_f = 0.27) by coupling between nitrobenzene (R_f = 0.8–0.9) and 4-aminophenol (R_f = 0.35–0.4) (TLC ran in 10% EtOAc in petroleum ether)

ii. On acidification the azo dye precipitates out.
iii. Collect the precipitates through filtration using a 35 mL G4 sintered funnel lined with ashless filter paper and dry to obtain the azo dye.

b. For water soluble dyes: Synthesis of (*E*)-4-((4-Hydroxyphenyl)diazenyl)benzenesulfonic acid (3b).
i. Neutralize the reaction mixture with 6 N HCl (~1.5 mL). In this case, the azo dye remains in the aqueous solution while the aromatic amine precipitates out.
ii. Filter using a sintered funnel lined with filter paper to separate the excess amine.
iii. Transfer the filtrate to a separating funnel and wash with 2 × 5 mL of ethyl acetate to remove any traces of amine.
iv. Concentrate the aqueous part in a rotary evaporator under reduced pressure (15 mbar) to obtain a crude mass. This step takes about 20 min.

Note: For step 7a (i), the acidic pH ensures complete precipitation of water-insoluble azo dye, **3a**. The initial change in pH was checked by litmus paper and the final pH of the solution by a pH meter to ensure there is no loss of product.

Note: Step 7b. (i): At this stage, the water-soluble dye remains in aqueous solution and excess amine precipitates out. The precipitated amine can be recovered through filtration and is sufficiently pure to be reused if required. If the aromatic amine is liquid directly proceed to step 7b (iii) after neutralization.

Purification

Timing: ~2 h

In this final step, the isolated azo dyes are further purified to remove any trace impurities and obtain pure product.

8. The crude compound obtained is further purified by recrystallization.
a. For water-insoluble dyes.
i. Add 2 mL EtOH:H_2O (1:4) to 50 mg crude product and heat on a water bath until the product is completely dissolved.
ii. Allow the solution to cool at room temperature It takes about 40–50 min.
iii. Collect the pure azo dye through filtration

b. For water soluble dyes.
   i. Dissolve the crude azo dye in absolute ethanol (5 mL) by heating.
   ii. Filter the solution while hot to remove any inorganic residue (KCl formed during neutralization).
   iii. Concentrate the ethanol under reduced pressure to obtain sufficiently pure azo dye.

Note: Step 8b (iii): A second recrystallization step in rectified spirit may be performed.

EXPECTED OUTCOMES

This protocol allows the synthesis of a variety of unsymmetrical azo dyes in a single step by coupling nitroarenes with aromatic amines. The use of microwave irradiation greatly enhances the reaction rate, and as such the synthesis of azo dyes was completed within a few minutes. By varying substituents in both nitroarenes and aromatic amine derivatives, a broad scope was established. A few commercial and water-soluble dyes were also generated following the above-mentioned protocol. Following this protocol bright yellow azo dye, Solvent yellow 7 (**3a**) and water soluble azo dye **3b** were isolated in 97% (92%) and 95% (91%) yields, respectively. Each reaction was conducted three times in identical conditions and the deviation in % of yield was within 1%.

Note: The yields provided in the parenthesis are the isolated yields after recrystallization.

Gram-scale synthesis

For the gram-scale synthesis 10 mmol of nitroarenes and 25 mmol of aromatic amine were taken in a larger microwave vessel (35 mL). The volume of solvent was reduced to 6 mL of EtOH-H_2O (2:1), 1.8 g of KOH was added and the reaction mixture was microwaved at 150 °C for 3 min. The gram scale synthesis was carried out for both water insoluble (**3a**) and water soluble dyes (**3b**). The isolated yields for **3a** and **3b** are found to be 95% and 89%, respectively. The reduction in the volume of the solvent nominally affects the yield or the reaction time.

Analytical data

(*E*)-4-(Phenyldiazenyl)phenol, **3a**[20]: bright yellow solid, 97%, m.p. 152–153°C [Lit. m.p. 149–151°C]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.86 (m, 4H), 7.53–7.42 (m, 3H), 6.94 (d, *J* = 8.0, 2H), 5.32 (s, 1H, exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 152.7, 147.2, 130.5, 129.1, 125.0, 122.6, 115.8; Elemental analysis: calcd (%) for $C_{12}H_{10}N_2O$: C, 75.16; H, 4.91; N, 16.23; found: C 74.78, H 4.84, N 16.03.

(*E*)-4-((4-Hydroxyphenyl)diazenyl)benzenesulfonic acid, **3b**[20]: red solid, 95%, m.p. >260 °C (charred) [Lit. m.p. > 250 °C]; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.16 (s, 1H, exchangeable), 7.73–7.64 (m, 4H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 157.7, 132.1, 132.0, 129.1, 124.8, 122.8, 116.5; Elemental analysis: calcd (%) for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07; found: C 51.91, H 3.67, N 10.02.

LIMITATIONS

Following this protocol the synthesis azo dyes with strong electron donating groups in both the aromatic rings is a challenge. For example, the reaction between 4-nitrophenol and 4-aminophenol did not produce the desired azo dye. The protocol also utilizes 2.5 equiv of amine for 1 equiv of nitroarenes. Some of the aromatic amines are expensive and the sacrifice of 1 equiv of the amine adds to the overall cost of the process.

TROUBLESHOOTING

Problem 1

In the case of halonitroarenes, the partial nucleophilic substitution of the halo group cannot be avoided leading to the formation of two products.

Potential solution

The nucleophilic substitution was most notable in the case of 4-chloronitrobenzene leading to the formation of the corresponding phenolic –OH containing azo dye as the by-product. In such cases, purification by column chromatography is to be performed. The nucleophilic substitution can be minimized by reducing the time of the reaction. 3 min was found to be the ideal time for completion of such reactions with a small amount of by-product from nucleophilic substitution.

Problem 2

The presence of strong electron donating groups (EDGs) in the nitroarenes and strong electron withdrawing groups (EWGs) in the aromatic amines hamper the formation of the azo dyes.

Potential solution

The exchange of substituents, i.e., electron-rich aromatic amines and electron-deficient nitroarenes circumvent the aforementioned problem and afford the targeted azo dyes in high yields.

Problem 3

During microwave irradiation, a rapid pressure build-up is occasionally observed.

Potential solution

The rapid pressure building generally occurs due to rapid temperature increase and can be avoided by increasing the ramping time.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Amrita Chatterjee, amrita@goa.bits-pilani.ac.in.

Materials availability

The study did not generate any new materials. All materials used in the work were sourced from commercial resources.

Data and code availability

All data reported in this paper will be shared by the lead contact upon request.

This paper does not report original code.

Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

A.C. and M.B. conceived and supervised the project. A.T. and A.C. investigated and optimized the protocols presented in the paper. A.T., M.B., and A.C. wrote the manuscript. The NMR spectroscopic analysis was done by A.T., A.C., and M.B.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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