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^{t}BuONO-MEDIATED GREENER APPROACH FOR SYNTHESIS OF AZO DYES FROM IMIDAZOTHIAZOLES

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ABSTRACT

Efficient and green methodology for the synthesis of azo dyes has been achieved by reaction of aromatic amines with imidazothiazole in presence of tert-BuONO and ethylene glycol:water on ultrasound irradiation at room temperature within short reaction time. This technique plans to beat the restrictions and disadvantages of the conventional methods such as low temperature, use of acids, long reaction time.

Keywords: Green synthesis, room temperature, azo dyes, t-BuONO, ultrasound

INTRODUCTION

The heterocyclic compounds derived from nitrogen and sulfur have flexible frameworks for drugs development and design **[1]**.

Out of several fused aforesaid thaizoles, imadazo[2,1-b] thiazole is one of the most intensively studied class of aromatic five-membered fused heterocyclics, Thus, imadazo[2,1-b] thiazole moiety if it is present in any compound will show numerous biological activities such as anti-microbial, anti-fungal, anti-neoplastic **[2]**, anti-inflammatory, anti-cancer, anti-HIV, anti-hypertensive, anti-convulsant and anti-diabetic activities **[3]**.

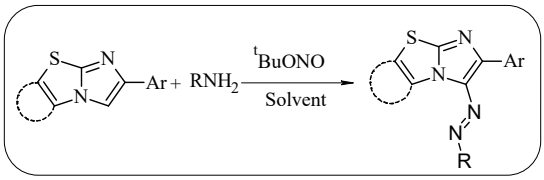
With the limited diazo coupling approaches on biologically relevant imidazo-heterocycles especially on imidazo thiazole ring and considering multi-tasking

applications of tert-butyl nitrite (TBN) **[4]** in organic synthesis, we have chosen to extrapolate novel research methodology against the existing one. It was believed that the new approach will overcome the drawbacks, mainly practical applicability for scale up reactions, mild and clean transformations across reported method.

Present work

Over the past decade, substantial progress has been achieved in the fields of diazo chemistry. Principally aromatic compounds holding 'azo/diazenyl' (R−N=N−R) are of profound importance due to their applications in organic synthesis, chemical industry and biological systems **[5, 6]**. They are used as radical reaction initiator, as ligands of metal complexes, therapeutic agents, and drug carrier **[7]**. Moreover they are well known to employ as colorants in the digital printing and photography **[8]**, new glassy materials **[9]**, liquid crystals **[10]**, chiral switches in photochemistry **[11]**, textile industries **[12]**, in dying of food, cosmetic, drug, biomedicine **[13]** and molecular recognition **[14]**. Due to their significance, chemistry has received immense attention. In fact, it is one of the promising areas of current research interest where researchers are paid their attention to synthesize these compounds *via* simple and ecofriendly methodologies.

With this background and because of our interest in ecofriendly synthesis of azo derivatives of thiazoles **[15]**, we sought to investigate the potential of arylhydrazine hydrochlorides as the aryldiazene source for diazenylation of C-H active compounds in the presence of tert. butyl nitrite under air **(Scheme 1)**.



Scheme 1

MATERIALS AND METHODS

Unless stated otherwise, reactions were conducted in oven-dried glasswares using anhydrous solvents (freshly distilled and dried over 4° molecular sieves). Reactions were performed at 0°C to room temperature (rt, approximately 25°C) and monitored using thin-layer chromatography (TLC) on commercial silica gel plates (GF254). Visualization of the developed plates was performed under UV light (254 nm). IR spectras were recorded with a Perkin-Elmer one FTIR spectrophotometer in which samples were examined as KBr discs~5% *w*/*w*. ^{1}HNMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution on

a BRUKER AVANCE (400) spectrometer, and chemical shifts are expressed as δ using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000. Elemental analyses were carried out at the Micro analytical centre of Shivaji University. The imidazo thiazole **(Table 2, 1a-c)** were prepared as previous reported **[16]**.

Typical experimental procedure for azo coupling:

A mixture of aniline 2a (0.22 mmol, 21 mg) and ^{t}BuONO (0.24 mmol, 25 mg, 29 µL) in DEG (1.5 mL) was placed in a round bottom flask and was sonicated for 3 min at room temperature. To this solution imidazo[1,2-a] thiazole 1a (0.20 mmol, 42 mg) was added and allowed to stir for 15-20min (TLC). The orange precipitate was collected, washed with EtOH (5 mL) and 10% ethyl acetate/petroleum ether (3 mL). The solid product was dried under vacuum to afford pure diazo product.

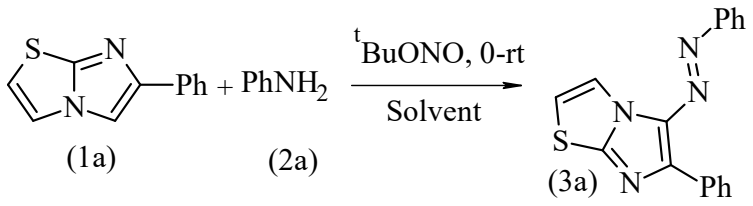
RESULTS AND DISCUSSION

In order to expand the richness of green synthetic methods, we focused to employ ultrasonic irradiation to hunt for atom-economical and easy-to-obtain diazo intermediates. In addition, greeting of optimal aqueous media as the main, if not exclusive reaction medium for organic transformations represents a safe, non-toxic, cheap and environmentally friendly alternative. In this regime our initial effort focused to optimize best reaction condition. To probe the envisaged objective, in a pilot experiment we examined the reaction between imidazo[1,2-a]thiazole (1a, 1.0 equiv.) and aniline (2a, 1.1 equiv.) in the presence of tert. butyl nitrite (100 mol %), in water as reaction medium under air at 0°C to room temperature affording the diazo compound 3a in 28% **(Table 1, entry 1)**. Next we checked the effect of various water miscible solvents like *N,N*-dimethyl formamide, ethylene glycol, acetonitrile, tetrahydrofuran, 1,4-dioxane, methanol and ethanol **(Table 1, entries 2-8)**. Among them, ethylene glycol:water combination was found to be the best to furnish the desired product with 81% yield after 10 min **(Table 1, entry 8)** probably due to fact that both polar protic solvent which helps to stabilize the diazonium ion. Further prolonged reaction time as well as manipulation in amine and ^{t}BuONO ratio did not improve the yield **(Table 1, entries 9-10)**.

Having established the optimized conditions, a series of diazo compounds were prepared by reacting imidazo[2,1-b]thiazole with a wide range of anilines with diverse substituent patterns. The results of reactions are summarized in **Table 2**. The reactions proceeded smoothly in all cases affording the desired products in good yields. Several sensitive functionalities such as OMe, Me, NMe_2 on

both **(Table 2, entries 1-10)** imidazo[2,1-b]thiazole as well as aniline nucleus were unaffected under the reaction conditions. The reactions of heteroaromatic amine **(Table 2, entries 5-6)** as well as electron deficient anilines **(Table 2, entry 3)** gave comparatively poor yields. All the synthesized azo dyes are known compounds and were characterized by comparing their melting point, IR, ^{1}H NMR, ^{13}C NMR and mass spectra with those found in the literature.

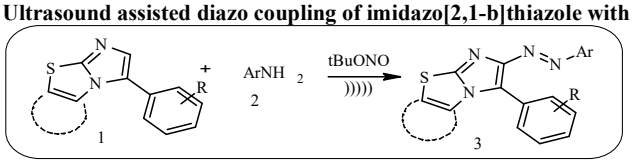
Table 1: Optimization in diazo coupling reaction condition[a]

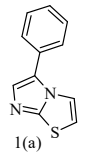
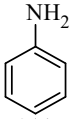
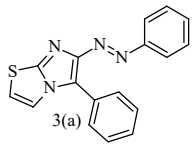
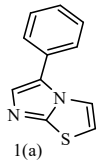
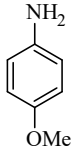
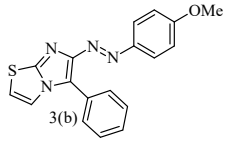
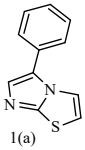
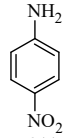
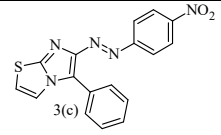
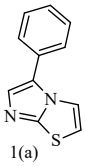
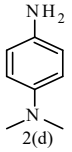
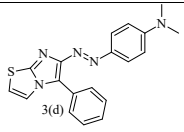
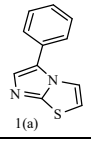
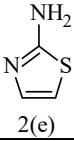
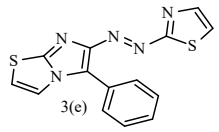
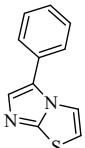
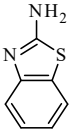
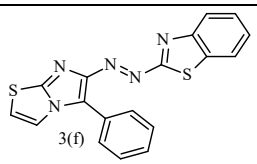
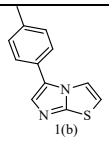
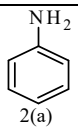
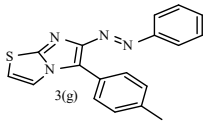
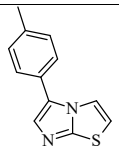
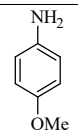
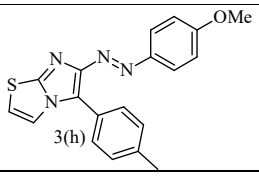
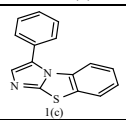
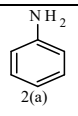
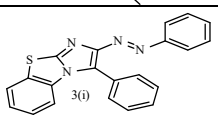


Sr. No.	Solvent	2a	^{t}BuONO	Time (min)	% Yield[b]
1	H_2O	1.0	1.1	15	28
2	DMF: H_2O (1:1)	1.0	1.1	15	65
3	ACN: H_2O (1:1)	1.0	1.1	15	50
4	THF: H_2O (1:1)	1.0	1.1	15	57
5	Dioxane: H_2O (1:1)	1.0	1.1	15	42
6	EtOH: H_2O (1:1)	1.0	1.1	15	75
7	MeOH: H_2O (1:1)	1.0	1.1	15	72
8	DEG: H_2O (1:1)	1.0	1.1	10	81
9	DEG: H_2O (1:1)	1.2	1.1	20	81
10	DEG: H_2O (1:1)	1.0	1.5	10	80

[a] Reaction conditions: 1a (0.1 mmol), 2a (0.1 mmol) and ^{t}BuONO (0.11 mmol) in DEG:Water (1:1 mL) were sonicated at 0-rt for 10-40 min. [b] Isolated yield.

Table 2: Ultrasound assisted diazo coupling of imidazo[2,1-b]thiazole with amines[a]



Sr. No.	(1)	'Ar' (2)	Product[b] (3)	Reaction time(min)	% Yield[b]	MP ºC
1	 1(a)	 2(a)	 3(a)	10	81	180-182
2	 1(a)	 2(b)	 3(b)	8	83	156-158
3	 1(a)	 2(c)	 3(c)	25	60	208-210
4	 1(a)	 2(d)	 3(d)	9	85	175-176
5	 1(a)	 2(e)	 3(e)	20	70	154-156
6	 1(a)	 2(f)	 3(f)	20	72	164-166
7	 1(b)	 2(a)	 3(g)	11	82	172-174
8	 1(b)	 2(b)	 3(h)	10	85	142-144
9	 1(c)	 2(a)	 3(i)	15	79	164-166

[a] Reaction conditios: 1 (0.1 mmol), 2 (0.1 mmol) and [t]BuONO (0.11 mmol) in DEG:Water (1:1 mL) were sonicated at 0ºC-rt for 10-40 min. [b] Isolated yield

CONCLUSION

In conclusion, we have developed an ultrasound assisted simple and efficient methodology to synthesize azo imidazo[2,1-b]thiazole derivatives using ter. butyl nitrite as a catalyst in air. The influence of ultrasound on reaction is not well understood; however, using ultrasound, diazo coupling were obtained faster than other existing methods. The easy formation of substituted azo dyes from inexpensive starting materials makes this process as a viable alternative to more traditional diazotization processes. Also present work attributes scope for extension to variety of substrates with various functional groups, without purification step, saving time, reducing energy and wastes, featuring an environmentally friendly method. Thus, the current method is an important contribution to the field, considering the potential synthetic, therapeutic and industrial application of these compounds.

4.6 Spectral data for the selected compounds

5-phenyl-6-[(E)-phenyldiazenyl]imidazo[2,1-b][1,3]thiazole (3a)

Orange solid**,** yield 82%

IR (KBr): υ=3071.3, 3004.2, 2907.3, 1587.8, 1558.0, 1513.3, 1408.9 1244.9, 984.0, 857.3 cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$): δ 7.80 (m, 3H), 7.76 (m, 2H), 7.65 (m, 2H), 7.49 (m, 4H), 7.28 (d, 1H), 7.1 (m, 1H).

^{13}CNMR (100MHz, $CDCl_3$):δ162.1, 158.0, 150.4, 147.3, 133.4, 132.4, 129.6, 129.2, 128.2, 128.0, 127.9, 126.3, 122.2, 117.5, 114.4, 101.6.

Elemental Analysis requires: C 67.08, H 3.97, N 18.41%.

$C_{17}H_{12}N_4S$: found: C 66.98, H 3.90, N 18.47%.

MS: m/z = 305.36(M+1).

6-[(E)-(4-methoxyphenyl)diazenyl]-5-phenylimidazo[2,1-b][1,3]thiazole (3b)

Yellow solid**,** yield 83%

IR (KBr): υ=3041.5, 2922.2, 1625.1, 1599.0, 1461.1, 1312.6, 1215.1, 980.3, 767.2 cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.88 (m, 3H), 7.57 (m, 3H), 7.50 (t, 1H), 7.15 (m, 1H), 6.90 (t, 1H), 3.88 (s, 3H).

^{13}CNMR (100MHz, $CDCl_3$) δ176.4, 162.9, 157.5, 149.9, 147.2, 134.9, 133.6, 131.7, 130.9, 129.7, 128.5, 128.1, 127.6, 117.4, 115.9, 114.5, 106.9, 55.4.

Elemental Analysis requires: C 52.92, H 3.95, N 27.43%.

$C_{18}H_{15}N_4OS$: found: C 52.85, H 3.90, N 27.47%.

MS: m/z = 335.09 (M+1).

6-[(E)-(4-nitrophenyl)diazenyl]-5-phenylimidazo[2,1-b][1,3]thiazole (3c)

Yellow solid**,** yield 60%

IR (KBr): υ=3127.5, 3049.4, 2981.94, 2935.2, 1597.7, 1519.6, 1356.6. cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$): δ 7.0-7.83 (m, 4H), 7.58-7.28 (m, 6H), 7.19 (t, 1H),

^{13}CNMR (100MHz, $CDCl_3$):δ 162.9, 157.9, 150.3, 147.2, 133.5, 131.7, 129.7, 129.2, 128.4, 128.1, 127.7, 126.8, 123.4, 117.6, 114.3, 101.8.

Elemental Analysis requires: C 58.44, H 3.17, N 20.05%.

$C_{17}H_{11}N_5O_2S$: found: C 59.01, H 3.20, N 20.07%.

MS: m/z = 350.36(M+1).

***N,N*-dimethyl-4-[(*E*)-(5-phenylimidazo[2,1-*b*][1,3]thiazol-6-yl)diazenyl]aniline (3d)**

Orange solid**,** yield 85%

IR (KBr): υ= 3120.5, 3041.4, 2972.9, 2929.2, 1589.7, 1511.6, 1346.7. cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$): δ 7.90 (m, 2H), 7.83 (m, 1H), 7.75 (m, 2H), 7.55 (m, 3H), 7.48 (t, 1H), 7.15 (t, 1H), 6.71 (d, 2H), 3.06 (s, 6H).

^{13}CNMR (100MHz, $CDCl_3$):δ 163.7, 156.9, 152.3, 149.5, 147.0, 133.7, 129.7, 129.0, 128.5, 128.1, 127.4, 117.4, 114.0, 111.5, 110.3, 107.2, 40.0.

Elemental Analysis requires: C 65.68, H 4.93, N 20.16%.

$C_{19}H_{17}N_5S$: found: C 65.58, H 4.90, N 20.14%.

MS: m/z = 348.43(M+1).

5-phenyl-6-[(E)-1,3-thiazol-2-yldiazenyl]imidazo[2,1-b][1,3]thiazole (3e)

Yellow solid**,** yield 70%

IR (KBr): υ=3115.0, 3105.5, 3051.4, 2951.94, 2939.2, 1601.7, 1505.6, 1346.6. cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$): δ 8.25 (m, 3H), 8.15 (t, 2H), 7.45 (d, 2H), 7.0 (d, 2H).

^{13}CNMR (100MHz, $CDCl_3$):δ 168.4, 166.0, 165.5, 164.4, 159.2, 137.6, 136.0, 129.2, 128.0, 127.6, 117.2, 114.5, 113.5.

Elemental Analysis requires: C 54.00, H 2.91, N 22.49%.

$C_{14}H_9N_5S_2$: found: C 54.08, H 2.90, N 22.14%.

MS: m/z = 313.38(M+1).

2-[(E)-(5-phenylimidazo[2,1-b][1,3]thiazol-6-yl)diazenyl]-1,3-benzothiazole (3f)

Yellow solid**,** yield 72%

IR (KBr): υ= 3105.5, 3041.4, 2951.9, 2933.2, 1591.7, 1519.6, 1356.6 cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$): δ 7.88 (m, 3H), 7.58 (m, 4H), 7.52 (t, 1H), 7.45 (m, 1H), 7.28 (s, 1H), 7.18 (m, 1H), 6.94 (m, 1H).

^{13}CNMR (100MHz, $CDCl_3$):δ 162.4, 157.5, 156.7, 151.0, 147.5, 133.7, 136.4, 129.6, 128.2, 126.4, 120.0, 115.6, 117.7, 114.5, 107.7, 106.3.

Elemental Analysis requires: C 59.81, H 3.07, N 19.38%.

$C_{18}H_{11}N_5S_2$: found: C 60.00, H 3.17, N 19.18%.

MS: m/z = 362.44(M+1).

5-(4-methylphenyl)-6-[(E)-phenyldiazenyl]imidazo[2,1-b][1,3]thiazole (3g)

Yellow solid**,** yield 82%

IR (KBr): υ=3109.0, 3102.0, 3090.9, 1606.68, 1588.9, 1560.7, 1319.8, 1304.1 cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$): δ 8.86 (m, 4H), 7.62 (m, 4H), 7.52 (m, 2H), 7.16 (m, 1H), 2.03 (s, 3H).

^{13}CNMR (100MHz, $CDCl_3$) δ176.4, 162.1, 158.0, 150.5, 147.3, 138.0, 134.9, 131.7, 130.9, 129.5, 128.3, 127.9, 121.9, 117.6, 114.4, 106.7, 20.4.

Elemental Analysis requires: C 52.92, H 3.95, N 27.43%.

$C_{19}H_{17}N_4OS$: found: C 52.85, H 3.90, N 27.47%.

MS: m/z = 349.11 (M+1).

6-[(E)-(4-methoxyphenyl)diazenyl]-5-(4-methylphenyl)imidazo[2,1-b][1,3]thiazole (3h)

Orange solid**,** yield 85%

IR (KBr): υ= 3110.7, 3055.1, 2961.9, 2931.2, 1592.1, 1517.8, 1342.6 cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$) : δ 7.68 (m, 3H), 7.53 (m, 4H), 7.43 (m, 1H), 7.10 (d, 1H), 7.01 (t, 1H), 3.95 (s, 3H); 1.86 (s, 3H).

^{13}CNMR (100MHz, $CDCl_3$):δ 162.3, 148.6, 146.6, 137.7, 129.5, 129.4, 128.1, 127.5, 117.3, 113.8, 112.9, 44.5, 22.5.

Elemental Analysis requires: C 65.50, H 4.63, N 16.08%.

$C_{19}H_{16}N_4OS$: found: C 65.55, H 3.60, N 16.00%.

MS: m/z = 349.41 (M+1).

3-phenyl-2-[(E)-phenyldiazenyl]imidazo[2,1-b][1,3]benzothiazole (3i)

Yellow solid**,** yield 79%

IR (KBr): υ= 3115.5, 3011.6, 2971.9, 2929.2, 1595.2, 1510.1, 1340.6 cm^{-1}

^{1}HNMR (400MHz, $CDCl_3$): δ 7.88 (m, 2H), 7.80 (m, 1H), 7.52 (m, 4H), 7.28-7.17 (m, 6H), 6.94 (d, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ162.8, 158.3, 157.5, 149.6, 147.0, 137.2, 129.4, 129.5, 128.3, 127.2, 126.4, 116.9, 115.7, 114.5, 113.6, 106.7.

Elemental Analysis requires: C 71.16, H 3.98, N 15.81%.

$C_{21}H_{14}N_4S$: found: C 71.10, H 3.90, N 16.00%.

MS: m/z = 355.42 (M+1).

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