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Saccharin: a cheap and mild acidic agent for the synthesis of azo dyes *via* telescoped dediazotization

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Abstract: Green synthesis methods are considered as a safer alternative to the conventional synthetic processes due to their eco-friendly nature, cost-effectiveness, and easy handling. In the present study, an eco-friendly and sustainable method for the synthesis of stable arenediazonium has been developed using saccharin as a cheap and mild acidic agent and *tert*-butyl nitrite as a diazotization reagent for the first time. These stable intermediates were used in the azo coupling reaction with 4-hydroxybenzaldehyde *via* telescoped dediazotization. The current method has advantages such as reduced waste by avoiding solvent for the purification of intermediate in diazotization step, cost-effectiveness, simple experimental procedure, good yield of azo dyes, metal-free waste, and environmentally benign conditions. An interesting aspect of this study is the recovery of saccharin from the reaction, which could be reused.

Keywords: azo coupling; cost-effectiveness; saccharin; stable arenediazonium; sustainable protocol.

1 Introduction

The reduction of environmental, human health, and safety risks of chemicals and synthetic procedures is the foremost goal of green chemistry, which can be achieved by redesigning toxic molecules, synthetic routes, and industrial processes. Reducing the amount of waste generated in reactions, recycling certain reagents, improving energy

efficiency, minimizing potential accidents, preparing the biodegradable or recyclable products, using sustainable raw materials, and avoiding molecules linked to toxicity are some routes in green chemistry. New catalysts, low-risk solvents, and reagents as well as new experimental processes are developed by green chemistry researches [1].

Azo compounds have gained broad applications in pharmaceutical, cosmetic, food, and dyeing/textile industry and analytical chemistry due to their specific physicochemical and biological properties. These compounds have shown potential in areas of nonlinear optics and electronics, drug delivery, chemosensors, liquid crystals, photochemical molecular switches, molecular shuttles, nanotubes, and optical storage media and in the preparation of protective eye glasses and filters [2]. Azo dyes also exhibit a variety of interesting antibiotic, antifungal, and anti-HIV activities [3]. The azo compounds were studied as a definitive diagnosis of Alzheimer's disease *via* imaging of amyloid plaques in the brain of patients with Alzheimer's disease [4].

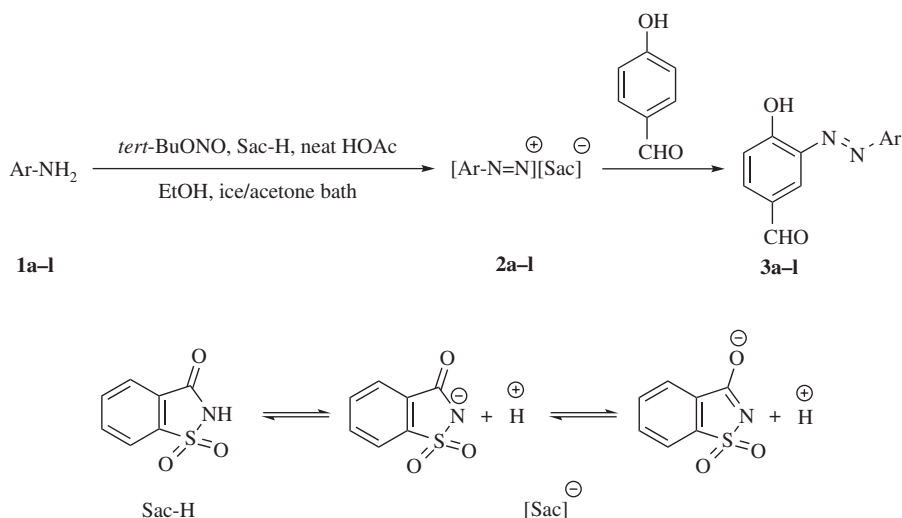
Saccharin (Sac-H) ($pK_a=1.31$) [5] is a cheap artificial sweetener and a calorie-free additive that was widely used in the food and drug industries [6]. The saccharin ring moiety has obtained considerable attention in the past decades as a key structural element in several biologically active compounds ranging from enzyme inhibitors to receptor ligands such as leukocyte elastase inhibitors and 5-HT_{1A} agonists [7]. *N*-substituted saccharin derivatives proved to be atypical and selective inhibitors of four different isoforms of human carbonic anhydrase (hCA I, II, IX, and XII). The results represent that most of them inhibited cancer-related human carbonic anhydrase *viz.* hCA XII and hCA IX, whereas they were poorly active against hCA II and hCA I [8–11].

The azo coupling reaction is an important procedure for the synthesis of azo compounds because the variety of the coupling and diazo components can be used and an enormous range of possible azo compounds can be produced [2].

The ability to couple the unstable intermediates into a subsequent consuming reaction step drastically increases the safety profile of many organic transformations [1, 12, 13]. The arenediazonium salts have shown particular

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Scheme 1: Modified Knoevenagel's method for synthesis of 4-hydroxy-3-[(*E*)-aryldiazenyl]-benzaldehyde derivatives *via* stable arenediazonium saccharinates.

versatility as reactive intermediates, which are prepared and directly reacted in a subsequent process in flow synthetic processes [14–17]. Most arenediazonium salts in dry state are potentially explosive chemicals; therefore, extreme care should be applied in handling/storing these intermediates, and it is well known that the nature of their counter-anion plays an important role on their stability [2, 18]. However, these arenediazonium salts have some drawbacks, and the development of an efficient and cost-effective reagent seems required.

Our ongoing researches are intended to develop new catalysts and reagents as well as procedures with higher energy efficiency to address an eco-friendly and sustainable method in organic transformations [19–21]. Recently, stable arenediazonium bis(trifluoromethane)sulfonimides were easily synthesized through diazotization of aniline derivatives with *tert*-butyl nitrite in the presence of bis(trifluoromethane)sulfonamide and glacial HOAc [22]. Bis(trifluoromethane)sulfonamide is commercially available but is expensive. Based on the structural similarity of *o*-benzenedisulfonimide and saccharin, we were interested to explore the potential of saccharin as an inexpensive and safe reagent for the generation of stable arenediazonium saccharin salts from aryl amines. To our pleasant surprise, the investigations clarified that this prediction is correct and the synthesis of azo coupling can be efficiently performed in high yield in one-pot synthesis by using stable arenediazonium saccharin intermediates. Then the diazotization reaction was followed with azo coupling reaction (Scheme 1). *Tert*-Butyl nitrite was chosen as the diazotizing reagent because it does not involve metal wastes as do NaNO_2 and therefore greatly lowers the risk of pollution

and also sodium nitrite does not meet the requirements of green chemistry in strongly acidic solutions. The mixture of saccharin and neat acetic acid was utilized as a cheap and mild acidic medium, thus the aniline derivatives containing acid-sensitive functional group can be tolerated. In order to reduce the amount of waste, the diazonium intermediates were not isolated and purified; the reaction was done *via* the telescopic procedure.

2 Materials and methods

2.1 Materials

Unless specified, all chemicals were of analytical grade and purchased from Merck (Merck Malaysia, Selangor Darul Ehsan, Malaysia) Aldrich, and Fluka Chemical Companies and used without further purification. Products were characterized by their physical constant and FT-IR, NMR, and elemental analysis. The purity determination of the substrates and reaction monitoring were accompanied by TLC using silica gel SIL G/UV 254 plates (Macherey-Nagel Sarl, Hoerdt, France).

2.2 Instrumentation

The purity determination of the products was accomplished by GC-MS on an Agilent 6890GC/5973MSD analysis instrument (Agilent Technologies, Santa Clara, USA) instrument under 70-eV conditions. The FTIR spectra were recorded on a Perkin Elmer 781 Spectrophotometer (Perkin Elmer, Seer Green, UK) using KBr pellets for solid and neat for liquid samples in the range of 4000–400 cm^{-1} . In all the cases, ^1H and ^{13}C NMR spectra were recorded with Bruker Avance 300 MHz

instrument [Bruker (Malaysia) Sdn. Bhd., Selangor, Malaysia]. All chemical shifts are quoted in parts per million (ppm) relative to TMS using deuterated solvent. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer (PerkinElmer, Inc., Waltham, MA, USA). Melting points were recorded on a Büchi B-545 apparatus [Mettler-Toledo (M) Sdn. Bhd., Selangor, Malaysia] in open capillary tubes. The high-resolution mass spectra of the products were recorded using an Agilent 6560 iFunnel Q-TOF LC-MS instrument (Agilent Technologies, Santa Clara, USA).

2.3 Typical procedure for the synthesis of azo compounds

Saccharin (Sac-H) (0.37 g, 2.0 mmol), glacial acetic acid (0.12 ml, 2.1 mmol), and *tert*-butyl nitrite (0.30 ml, ~2.3 mmol) were stirred in dry ethanol (10 ml) for 5 min at low temperature in an ice bath. Then aryl amine (**1a–l**) (0.19 ml, 2.0 mmol) was added dropwise over 5 min, and stirring was gently continued at low temperature until the aryl amine disappeared (monitored by TLC or color test of azo coupling with 2-naphthol). The solvent, by-product *tert*-BuOH, and excess *tert*-BuONO were evaporated under reduced pressure. Next, a solution of 4-hydroxy benzaldehyde (2 mmol) in ethanol (5 ml) containing the appropriate amount of K₂CO₃ (0.55 g, 4 mmol) was added in one portion to the intermediate of **2(a–l)**, and the mixture was stirred in an ice bath for the period of time mentioned in Table 1 (Scheme 1). After completion of reaction (confirmed by a negative test of azo coupling with 2-naphthol), the reaction mixture was poured into boiling water (15 ml); then the aqueous layer was separated. The organic layer was washed with brine (3×5 ml), and the brine layer was extracted with

EtOAc (2×2 ml). The combined organic layer was dried over Na₂SO₄ and filtered. The solvent was evaporated by rotary under reduced pressure, and the solid product was washed with *n*-hexane (3×2 ml) and dried overnight to produce the pure compound **3(a–l)**. To evaluate the recovery of saccharin, the residue white solid was eluted through a column of Dowex® 50WX8 hydrogen form, 200–400 mesh (Sigma-Aldrich) with water. Water was removed under reduced pressure, and saccharin was extracted with EtOAc (5×5 ml). The extracts were dried over anhydrous Na₂SO₄ and filtered. After evaporation of the solvent under reduced pressure, pure saccharin was recovered in 84–90% yield (0.31–0.33 g), which was then reused to prepare the diazonium saccharinates. All known products were identical with respect to the melting point, FTIR, and NMR spectra to those previously reported [22]. 4-Methoxybenzenediazonium saccharinate (**2j**) was stable to be kept in the refrigerator (4°C) for 1 week without any loss of activity.

Caution. It is noteworthy to mention that diazonium salts in the dry state are potentially explosive and they must be cautiously stored and handled.

Physical and spectral data of 4-methoxybenzenediazonium saccharinate (2j): m.p. 141–143°C; FT-IR (KBr) ν_{\max} = 3084 ($\nu_{\text{C-Harom}}$), 2918, 2883 ($\nu_{\text{C-H}}$), 2303 ($\nu_{\text{N=N}}$), 1732 ($\nu_{\text{C=O saccharin ring}}$), 1681, 1658, 1557 ($\nu_{\text{C=Carom}}$), 1339 ($\nu_{\text{asym SO}_2}$), 1320, 1250, 1173 ($\nu_{\text{sym SO}_2}$), 1075, 821 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆) δ = 3.81 (s, 3H, OCH₃), 7.04 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.89–7.95 (m, 1H, Ar-H), 8.31–8.38 (m, 2H, Ar-H), 8.42–8.49 (m, 1H, Ar-H) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆) δ = 55.5, 114.9, 123.6, 124.5, 126.7, 131.7, 135.2, 138.5, 147.1, 158.9, 163.3, 166.9 ppm; HRMS (+ESI): Calcd. for C₇H₇N₂O: 135.0553; Found 135.0557; HRMS (–ESI): Calcd. for C₇H₄NO₃S: 181.9917; Found 181.9924.

Table 1: Telescopic azo coupling reaction of the aniline derivatives with 4-hydroxybenzaldehyde at ice bath via modified Knoevenagel's method.^a

Entry	Ar-NH ₂ (1)	Product (3)	Azo coupling product (3)			m.p. (°C)	
			Diazonium saccharin salts (2)	Fresh	Stored ^b	Found	Reported (Ref. [22])
1	C ₆ H ₅ -	a	60	84	81	130–132	129–131
2	4-CH ₃ -C ₆ H ₄ -	b	60	82	79	136–137	138–140
3	2,6-[(CH ₃) ₂ CH]-C ₆ H ₃ -	c	90	67	65	148–150	148–150
4	4-Cl-C ₆ H ₄ -	d	60	83	81	136–137	134–136
5	2-Cl-C ₆ H ₄ -	e	50	82	80	134–136	134–136
6	4-Br-C ₆ H ₄ -	f	60	84	82	139–141	141–143
7	4-NO ₂ -C ₆ H ₄ -	g	60	92	88	139–142	139–141
8	2-NO ₂ -C ₆ H ₄ -	h	50	86	84	121–123	121–123
9	4-CH ₃ CO-C ₆ H ₄ -	i	60	84	80	152–154	156–158
10	4-CH ₃ O-C ₆ H ₄ -	j	65	81	78	148–150	148–150
11	3,4-(methylenedioxy) aniline	k	65	85	81	129–131	129–131
12	4-morpholineoaniline	l	60	77	74	120–122	121–123

^aReaction conditions: aniline derivatives (**1**) (2.0 mmol), *tert*-butyl nitrile (0.30 ml, ~2.3 mmol), saccharine (0.37 g, 2.0 mmol), and glacial acetic acid (0.12 ml, 2.1 mmol) in ethanol (10 ml); 4-hydroxybenzaldehyde (0.25 g, 2 mmol) in absolute ethanol (5 ml) containing K₂CO₃ (0.55 g, 4 mmol).

^bStored for 1 week at 4°C (refrigerator).

^cIsolated yield.

2.4 Physical and spectral data of azo coupling products

4-hydroxy-3-[(E)-phenyldiazenyl]benzaldehyde (3a): FT-IR (KBr) ν_{\max} = 3425, 1668, 1596, 1483 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 7.12 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.48–7.54 (m, 2H), 7.89 (d, J = 7.8 Hz, 2H), 8.17 (dd, J = 8.4 and 2.4 Hz, 1H), 8.20 (d, J = 2.4 Hz, 1H), 10.03 (s, 1H), 14.32 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_2^+$: 227.0815; Found 227.0812; Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.94; H, 4.39; N, 12.26.

4-hydroxy-3-[(E)-p-tolyldiazenyl]benzaldehyde (3b): FT-IR (KBr) ν_{\max} = 3426, 2986, 1686, 1598, 1482 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 2.47 (s, 3H), 7.23 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 8.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 8.07 (dd, J = 8.2 and 2.4 Hz, 1H), 9.95 (s, 1H), 14.30 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_2^+$: 241.0972; Found 241.0969; Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.91; H, 4.98; N, 11.58.

4-hydroxy-3-[(E)-(2,6-diisopropylphenyl)diazenyl]benzaldehyde (3c): FT-IR (KBr) ν_{\max} = 3234, 2927, 1675, 1591, 1458, 1437 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 1.17 (d, J = 6.0 Hz, 12H), 3.03 (quin, J = 6.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 7.17–7.32 (m, 3H), 7.87 (d, J = 8.0 Hz, 1H), 9.98 (s, 1H), 14.27 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_2^+$: 311.1754; Found 311.1751; Anal. Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.49; H, 7.09; N, 8.96.

4-hydroxy-3-[(E)-(4-chlorophenyl)diazenyl]benzaldehyde (3d): FT-IR (KBr) ν_{\max} = 3426, 1686, 1600, 1486, 750 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 7.02 (dd, J = 8.4 and 2.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 8.03 (d, J = 8.4 Hz, 1H), 9.95 (s, 1H), 14.30 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{13}\text{H}_{10}\text{ClN}_2\text{O}_2^+$: 261.0425; Found 261.0424; Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 59.81; H, 3.43; N, 10.69.

4-hydroxy-3-[(E)-(2-chlorophenyl)diazenyl]benzaldehyde (3e): FT-IR (KBr) ν_{\max} = 3396, 1676, 1610, 1482, 739 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 7.08 (dd, J = 8.4 and 2.0 Hz, 1H), 7.26 (td, J = 8.0 and 1.0 Hz, 1H), 7.37 (td, J = 8.0 and 1.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 8.0 and 2.0 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 8.0 and 1.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 9.93 (s, 1H), 14.29 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{13}\text{H}_{10}\text{ClN}_2\text{O}_2^+$: 261.0425; Found 261.0421; Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}_2$: C, 59.90; H, 3.48; N, 10.75. Found: C, 59.86; H, 3.44; N, 10.71.

4-hydroxy-3-[(E)-(4-bromophenyl)diazenyl]benzaldehyde (3f): FT-IR (KBr) ν_{\max} = 3396, 1676, 1592, 1486, 687, 650 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 7.11 (dd, J = 8.4 and 2.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 2.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 8.4 Hz, 1H), 9.98 (s, 1H), 14.28 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{13}\text{H}_{10}\text{BrN}_2\text{O}_2^+$: 304.9920; Found 304.9917; Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{BrN}_2\text{O}_2$: C, 51.17; H, 2.97; N, 9.18. Found: C, 51.11; H, 2.83; N, 9.13.

4-hydroxy-3-[(E)-(4-nitrophenyl)diazenyl]benzaldehyde (3g): FT-IR (KBr) ν_{\max} = 3428, 1676, 1602, 1567, 1486, 1385, 1124 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 7.20 (dd, J = 8.2 and 2.0 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.4 Hz, 1H), 9.95 (s, 1H), 14.29 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_3\text{O}_4^+$: 272.0666; Found 272.0663; Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_4$: C, 57.57; H, 3.34; N, 15.49. Found: C, 57.47; H, 3.37; N, 15.52.

4-hydroxy-3-[(E)-(2-nitrophenyl)diazenyl]benzaldehyde (3h): FT-IR (KBr) ν_{\max} = 3385, 1665, 1595, 1546, 1481, 1379, 1118 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 7.50 (d, J = 8.0 Hz, 1H), 7.54–7.59 (m, 2H), 7.89–7.94 (m, 2H), 8.12 (d, J = 8.0 Hz, 1H), 9.96 (s, 1H), 14.24 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_3\text{O}_4^+$: 272.0666; Found 272.0661; Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_4$: C, 57.57; H, 3.34; N, 15.49. Found: C, 57.52; H, 3.31; N, 15.45.

4-hydroxy-3-[(E)-(4-acetylphenyl)diazenyl]benzaldehyde (3i): FT-IR (KBr) ν_{\max} = 3210, 2958, 2880, 1681, 1648, 1593, 1480, 1389, 1328, 1086 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 2.64 (s, 3H), 6.62 (dd, J = 9.0 and 2.6 Hz, 1H), 6.81 (d, J = 2.6 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.6 Hz, 2H), 9.95 (s, 1H), 14.23 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_3^+$: 269.0921; Found 269.0918; Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.09; H, 4.48; N, 10.42.

4-hydroxy-3-[(E)-(4-methoxyphenyl)diazenyl]benzaldehyde (3j): FT-IR (KBr) ν_{\max} = 3296, 2958, 2880, 1686, 1588, 1479, 1186 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 3.89 (s, 3H), 6.84 (dd, J = 8.8 and 2.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 8.8 Hz, 1H), 9.95 (s, 1H), 14.30 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}_3^+$: 257.0921; Found 257.0918; Anal. Calcd. for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.57; H, 4.78; N, 10.78.

4-hydroxy-3-[(E)-(3,4-(methylenedioxy)phenyl)diazenyl]benzaldehyde (3k): FT-IR (KBr) ν_{\max} = 3316, 2962, 2876, 1685, 1598, 1487, 1154 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 5.89 (s, 2H), 6.51–6.57 (m, 3H), 6.67 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 9.85 (s, 1H), 13.73 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_4^+$: 271.0713; Found 271.0709; Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.17; H, 3.69; N, 10.33.

4-hydroxy-3-[(E)-(4-morpholinophenyl)diazenyl]benzaldehyde (3l): FT-IR (KBr) ν_{\max} = 3421, 3014, 2873, 1686, 1597, 1485, 1285, 1125 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ = 3.25 (t, J = 4.8 Hz, 4H), 3.89 (t, J = 4.8 Hz, 4H), 7.01 (dd, J = 8.4 and 2.0 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 9.94 (s, 1H), 13.92 (s, 1H) ppm; HRMS (+ESI): Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3^+$: 312.1343; Found 312.1341; Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.53; H, 5.52; N, 13.43.

3 Results and discussion

The mixture of saccharin (Sac-H), glacial acetic acid, and *tert*-butyl nitrite in ethanol was slowly stirred for 10 min at low temperature (ice bath). Then aryl amine (**1a–l**) was added dropwise, and stirring was gently continued at low temperature until the aniline derivative disappeared (monitored by TLC and the color test of azo coupling with 2-naphthol). At a higher temperature, the reaction gave byproducts and several spots were observed on TLC. Finally, the arenediazonium saccharinate was added dropwise to the basic solution of 4-hydroxy benzaldehyde in ethanol to afford azo products. After work-up, pure saccharin was recovered

in 84–90% yield and was utilized to the synthesis of the diazonium saccharin salts. The arenediazonium saccharinate solutions (**2a–l**) were stable to be kept in the refrigerator (4°C) for 1 week without any loss of activity. When aniline was reacted under optimized conditions in the absence of saccharin, **3a** was not obtained, and this proved that saccharin plays a much more important role in the present reaction (monitored by GC-MS).

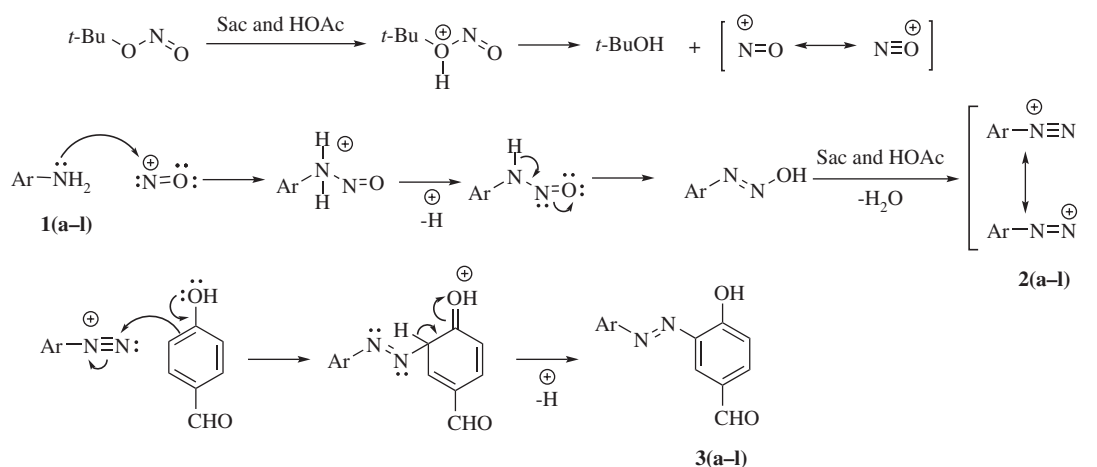
Whitehead and Traverso [23] prepared 3-amino-1,2-benzisothiazole-1,1-dioxides by refluxing saccharin with excess alkyl or aralkyl amines (no aryl amines) boiling at least at 130°C for more than 8 h. To the best of the authors' knowledge, there have been no reports presented on the reaction of saccharin and aryl amines at low temperature; however, a control experiment was carried out to investigate it. No 3-amino-1,2-benzisothiazole-1,1-dioxide was observed when saccharin, aniline, and glacial acetic acid were stirred in ethanol at room temperature for 1 h (GC-MS analysis), which signifies that the reaction did not proceed at all. Furthermore, it was reported that when thiosaccharin was treated with amines in methanol at room temperature, the alkyl or aryl ammonium saccharinates were obtained in good yields [24]. Therefore, it seems that aniline cannot act, as nucleophile attacks the C atom of the carbonyl group in saccharin to form 3-amino-1,2-benzisothiazole-1,1-dioxide.

In order to investigate the stability of the diazonium saccharinate in dry state, the dry 4-methoxyphenyldiazonium saccharinate (**2j**) was isolated in 88% yield in the diazotization step. This solid salt was dried at room temperature overnight and then was kept in the refrigerator (4°C) for 1 week. Then the basic solution of 4-hydroxybenzaldehyde was added to dry diazonium salt, which offered 78% yield of 4-hydroxy-3-[(*E*)-(4-methoxyphenyl)diazenyl]

benzaldehyde (**3j**). It seems that extensive delocalization of the charge over the -CO-N-SO₂- framework, assisted by the withdrawing inductive effect of the benzene ring, makes [Sac]⁻ anion and the corresponding salt highly resonance-stabilized [22].

Aryl amines (**1a–l**) containing electron-withdrawing and electron-donating substituents gave azo coupling products in good to excellent yields (Table 1, entries 2, 7, 9 and 10). As previously reported [22], there is no clear correlation between electronic effects of substituents on aromatic ring and reaction rate and yield (Table 1). It seems that electronic effect of the substituent at the first step is compensated in the second step (Table 1, entries 7, 9 and 2, 10). Steric effects of substituents on aryl amines decreased both the yield and the reaction rate; for example, *ortho*-substituent anilines and the sterically hindered aniline viz., 2,6-diisopropylaniline, offered lower yields within longer reaction times (Table 1, entries 3, 5 and 8). The hetero-anilines such as 3,4-(methylenedioxy) aniline and 4-morpholineoaniline also gave good yields under optimal conditions (Table 1, entries 11 and 12). The present method was successfully applied on a macro scale viz., 20 mmol of 4-methoxyaniline (**1j**) was converted into 4-hydroxy-3-[(*E*)-(4-methoxyphenyl)diazenyl]benzaldehyde (**3j**) in 75% isolated yield.

According to the plausible mechanism (Scheme 2), the nitoso cation (⁺N=O ↔ N≡O⁺) as a mild electrophile is produced from saccharin and *tert*-butyl nitrite in the first step. Then the nitrogen atom of aniline reacts with a nitoso cation (⁺N=O ↔ N≡O⁺) to form arenediazonium saccharin salt, which is greatly stabilized by resonance. The presence of such a delocalization was confirmed in the crystal structure of some of the sulfonamide salts [25]. Then an electrophilic substitution reaction occurs in the



Scheme 2: The diazotization process of aryl amines in presence of saccharin and *tert*-butyl nitrite, followed by azo coupling reaction with 4-hydroxybenzaldehyde.

second step. 4-Hydroxybenzaldehyde activated in mild basic medium react with diazonium cation in $[\text{ArN}_2]^+[\text{Sac}]^-$ salt followed by the loss of a proton to restore the aromaticity of the ring, and finally, the corresponding azo coupling product is afforded.

In order to compare, the intermediates of 4-methoxybenzenediazonium 4-methylbenzenesulfonate, *o*-benzenedisulfonimide, and bis(trifluoromethane)sulfonimide were obtained in 32% [4], 89% [26], and 90% [22] yield, respectively, whereas 4-methoxyphenyldiazonium saccharinate (**2j**) offered to yield 81% with the same amounts of reactants in the present method. *o*-Benzenedisulfonimide and bis(trifluoromethane)sulfonamide worked well for the preparation of stable arenediazonium salts; however, these reagents are too expensive for large-scale application. On the other hand, the synthesis of *o*-benzenedisulfonimide is very laborious and demands expensive, toxic, and fatal reagents [27].

4 Conclusion

In summary, an efficient and cost-effective telescopic catalyst-free reaction to the synthesis of azo compounds was developed by using *tert*-butyl nitrite and a mixture of saccharin and glacial acetic acid in ethanol mixed solvent followed by the azo coupling reaction with 4-hydroxybenzaldehyde. The stable arenediazonium saccharinates were stored for long periods of time and then were used without any loss of activity and ascertained threads. The current method has advantages such as reduced waste, cost-effectiveness, simple experimental and environmentally benign procedure, and good yield of the products with potential use as azo-dyes, pigments, and therapeutic agents and the reactants in heterocyclic synthesis.

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Graphical abstract

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Saccharin: a cheap and mild acidic agent for the synthesis of azo dyes via telescoped dediazotization

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Original article: A sustainable method for the synthesis of stable arenediazonium has been developed using saccharin and *tert*-butyl nitrite.

Keywords: azo coupling; cost-effectiveness; saccharin; stable arenediazonium; sustainable protocol.

