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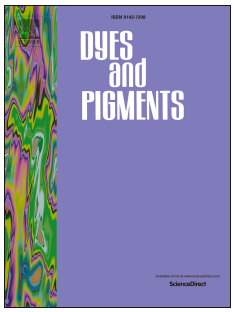

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CRediT authorship contribution statement

Mateja Mihelač: Methodology, Investigation, Writing - original draft.

Ana Siljanovska: Methodology, Investigation, Writing - original draft.

Janez Košmrlj: Conceptualization, Supervision, Funding acquisition, Writing - review & editing.

A Convenient Approach to Arenediazonium Tosylates

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Abstract

Herein we present a mild, simple and environmentally friendly diazotization protocol of aromatic and heteroaromatic anilines into stable diazonium salts that surpass previously reported procedures. The reaction proceeds with *tert*-butyl nitrite in the presence of an equimolar amount or small excesses of *p*-toluenesulfonic acid in ethyl acetate, at room temperature. *o*-Phenylenediamines yield benzotriazolium tosylates. The resulting diazonium tosylates proved to be bench stable over a long period of time. In selected examples, diazonium salts were let to react with activated aromatic compounds including 2-naphthol and aniline derivatives into the corresponding azo dyes.

Keywords: Diazotization, Diazonium salts, Azo compounds, *p*-Toluenesulfonic acid

1. Introduction

Aromatic diazonium salts are highly important building blocks in many fields of synthetic organic chemistry. Since their discovery by Griess [1] in 1858 these compounds have

played a role in named reactions including Sandmeyer, [2] Gomberg-Bachmann [3], Balz-Schiemann [4], and Meerwein [5], to name just a few. Wide utility in the synthesis of industrially important chromophores [6], modification of polymer, and nano-materials [7–10] as well as syntheses of new metallic and non-metallic materials are well documented [11,12]. Aromatic diazonium salts are excellent electrophiles or proelectrophiles, either directly through nitrogen coupling, or by releasing a dinitrogen molecule to form *in situ* aryl carbocation species. Noteworthy is their application in palladium catalyzed carbon-carbon and carbon-heteroatom coupling reactions, in which their "superelectrophilicity" is recognized as an advantage over aryl halides [13,14]. This high reactivity has enabled development of new metal-free carbon-carbon bond forming reactions [15,16]. Coupling reactions that involve diazonium salts as nitrogen electrophiles are crucial for the preparation of triazenes, potential antitubercular and antitumor agents [17,18,19] and synthetic equivalents of amines and diazonium salts [20,21]. Several radical reactions with diazonium salts are also well known and established as major pathways to synthetically useful molecules [22,23]. An extremely important industrial application of diazonium salts is the preparation of azo compounds, well known for their uses as organic dyes and pigments, pharmaceutical agents and food additives [24].

The propensity of aryl diazonium salts to undergo uncontrolled dediazotization pathways makes them unstable and potentially explosive. The stability is governed by the nature of substituents present at the aromatic ring with those having strongly electron-withdrawing character being less stable. In addition, also the access to those salts is more challenging because diazotization of weakly basic amines is difficult due to their low reactivity and solubility. In industrial process, the diazotization of weakly basic amines with sodium nitrite is conducted in the presence of large excess quantities of concentrated sulfuric acid as a solvent rising economic,

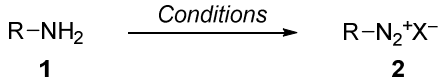
environmental and safety concerns. It produces high acid content wastewater. The strong dilution heat effect of concentrated sulfuric acid during the addition of sodium nitrite solution demands efficient cooling of the reaction mixture to control the temperature of the process. The above makes aryl diazonium salts with two or three strong electron-withdrawing functional groups, highly important for the preparation of deep-shade disperse azo dyes with excellent color fastnesses, challenging. The stability of diazonium salts can be greatly increased by the choice of counterions such as tetrafluoroborate, hexafluorophosphates, or disulfonimide [25].

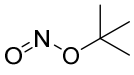
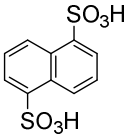
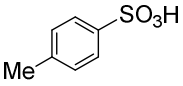
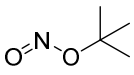
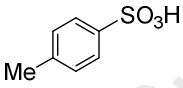
Recently, Tang and co-workers reported the synthesis of stable solid diazonium salts of weakly basic amines through diazotization by *tert*-butyl nitrite in the presence of excess amounts of 1,5-naphthalenedisulfonic acid as a proton donor and stabilizer of diazonium salts [24]. Although showing excellent stability profile, the obtained products existed as mixtures of mono- and di-aryldiazonium 1,5-naphthalenedisulfonates in the ratio that could not be predicted and/or controlled. Despite the mild reaction conditions used, with ethyl acetate as the reaction solvent, at room temperature, the relatively high price of 1,5-naphthalenesulfonic acid and undefined product composition render this method less attractive.

Arenediazonium tosylates reported by Filimonov, Chi and co-authors also exhibit great high thermal stability. However, although their procedure involves diazotization of anilines in the presence of cheaper *p*-toluenesulfonic acid, it utilizes polymer-supported nitrite [26]. The later was prepared by treating ion exchange of porous tetramethylammonium hydroxide resin AV-17-86 or Amberlyst A26 with an aqueous solution of $NaNO_2$, rendering the method less appealing.

71

72 **Fig. 1.** Representative diazotization methods.



	Nitrogen source	*Bronsted acid*	*Solvent and temp.*	*Product*
Tang *et al.* [24]:			EtOAc 50 °C then 25 °C	R = aryl, undefined salt composition: $HO_3S–R'–SO_3^-\ {}^+N_2–R$ + $R–N_2^+\ {}^-O_3S–R'–SO_3^-\ {}^+N_2–R$
Filimonov, Chi *et al.* [26]:	Resin-NO_2^-		AcOH, rt	R = aryl; X^- = TsO^-
This work:			EtOAc, rt	R = aryl, heteroaryl X^- = TsO^-

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74

75 High demand for a sustainable preparation of isolable and nonhazardous arenediazonium
76 salts prompted us to combine the above two methods into a truly practical protocol for the
77 synthesis of arenediazonium tosylates that proceeds in a green reaction solvent and at room
78 temperature by employing commercially available reagents. We selected *tert*-butyl nitrite as a
79 surrogate for nitrous acid ($NaNO_2$/HCl) because it is mild, easy to handle, commercially
80 available and inexpensive reagent of good solubility in organic solvents [27,28]. It has been
81 frequently used to generate arenediazonium salts *in situ* under safe conditions from small to bulk
82 multikilogram scale [29].

83

84 **2. Experimental section**

85 *2.1. Materials and instruments*

Starting materials and solvents were used as obtained from the commercial sources without further purification (Merck, Fluorochem, abcr).

Melting points were determined on a Leica Galen III micro hot stage and are uncorrected.

IR spectra were obtained with Bruker ALPHA FT-IR equipped with a Platinum ATR as a solid sample support.

NMR spectra were recorded with a Bruker Avance III 500 MHz NMR operating at 500 MHz (^{1}H), 471 MHz (^{19}F), and 126 (^{13}C) MHz at 296 K or with a Bruker DPX 300 spectrometer operating at 300 MHz (^{1}H) at 302 K. Proton spectra were referenced to the residual signals of $CHCl_3$ (at δ 7.26 ppm) and DMSO-d_5 (at δ 2.50 ppm). Carbon chemical shifts are given against the central line of the solvent signal: $CDCl_3$ (at δ 77.16 ppm), DMSO-d_5 (at δ 39.52 ppm). ^{19}F NMR spectra were referenced to CCl_3F and 15% BF_3 etherate in $CDCl_3$ as external standard at δ 0. Chemical shifts are given on δ scale (ppm). Coupling constants (J) are given in Hertz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broadened).

An Agilent 6224 time-of-flight (TOF) mass spectrometer equipped with a double orthogonal electrospray source at atmospheric pressure ionization (ESI) coupled to an Agilent 1260 HLPC was used for recording HRMS spectra. Mobile phase composed of two solvents: A was 0.1% formic acid in Milli-Q water, and B was 0.1% formic acid in acetonitrile mixed in the ratio of 1:1. Compounds were prepared by dissolving the samples in acetonitrile. 0.1–10 μL of each sample and injected into the LC-MS. Flow rate was 0.4 mL/min. Fragmentor voltage was 150 V. Capillary voltage 4000 V. Mass range 100–1700.

For radial chromatography, Chromatotron model 7924T was used. Silica gel 60 PF254 containing gypsum for preparative layer chromatography was used for glass radial

chromatography plates. Analytical thin-layer chromatography (TLC) was carried out on Fluka Silica Gel TLC cards, visualized with a UV lamp (254 nm and/or 366 nm).

*2.2. General procedure for diazotization of (hetero)arylamines **1a**–**1n**.*

In a round bottomed flask equipped with a magnetic stirrer, *p*-toluenesulfonic acid monohydrate (1–2.3 mmol) was dissolved in ethyl acetate (10 mL). Aniline (1 mmol) was added followed by dropwise addition of *tert*-butyl nitrite (1–6 mmol). The resulting mixture was stirred for 15 min at room temperature. For the synthesis of **2k** and **2l**, the reaction mixture was stirred for 1 h and 24 h, respectively. The product was filtrated, washed with ethyl acetate and air dried to give pure diazonium tosylate. The exceptions were crude products **2e** and **2f**, which were purified by recrystallization from acetone. Compound **2l** was oily and was isolated by evaporation of the solvent under reduced pressure.

*Benzenediazonium tosylate (**2a**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), aniline (**1a**, 95 mg, 1.00 mmol) and *tert*-butyl nitrite (356 µL, 3.00 mmol). The product was obtained as a dark pink solid (276 mg, 0.99 mmol, 99%). The data were in agreement with those from the literature [30]. Mp: 90.7–91.9 °C. IR: 3092, 2293, 1618, 1568, 1494, 1187 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 8.69–8.65 (m, 2H), 8.28–8.24 (m, 1H), 8.00–7.96 (m, 2H), 7.48–7.44 (m, 2H), 7.13–7.08 (m, 2H), 2.28 (s, 3H). HRMS (ESI+): calcd for $C_6H_5N_2^+$ $[M]^+$ *m/z* 105.0447; found: 105.0450.

The synthesis of product **2a** was also conducted on 4 mmol scale following the general procedure, employing *p*-toluenesulfonic acid monohydrate (760 mg, 4.00 mmol), ethyl acetate (15 mL), aniline (365 µL, 4.00 mmol) and *tert*-butyl nitrite (1425 µL, 12.00 mmol) to give diazonium tosylate **2a** (1.0151 g, 3.67 mmol, 92%).

*3,4-Dichlorobenzenediazonium tosylate (**2b**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 3,4-dichloroaniline (**1b**, 163 mg, 1.00 mmol) and *tert*-butyl nitrite (356 µL, 3.00 mmol). The product was obtained as a white solid (314 mg, 0.91 mmol, 91%). Mp: 144.3–145.5 °C. IR: 3105, 2288, 1551, 1445, 1223, 1170, 1029, 817, 678 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.08 (d, J = 2.4 Hz, 1H), 8.68 (dd, J = 2.4, 8.9 Hz, 1H), 8.28 (d, J = 8.9 Hz, 1H), 7.47–7.44 (m, 2H), 7.13–7.09 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 145.5, 145.1, 137.8, 133.7, 133.4, 133.2, 132.5, 128.1, 125.5, 115.9, 20.8. HRMS (ESI+): calcd for $C_6H_3Cl_2N_2^+$ $[M]^+$ *m/z* 172.9668; found: 172.9671.

The synthesis of product **2b** was also conducted on 4 mmol scale following the general procedure, employing *p*-toluenesulfonic acid monohydrate (760 mg, 4.00 mmol), ethyl acetate (30 mL), 3,4-dichloroaniline (**1b**, 648 mg, 4.00 mmol) and *tert*-butyl nitrite (1425 µL, 12.00 mmol) to give diazonium tosylate **2b** (1.2586 g, 3.65 mmol, 91%).

*4-Chloro-3-(trifluoromethyl)benzenediazonium tosylate (**2c**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 4-chloro-3-(trifluoromethyl)aniline (**1c**, 195 mg, 1.00 mmol) and *tert*-butyl nitrite (118.8 µL, 1.00 mmol). The product was obtained as a white solid (337 mg, 0.89 mmol, 89%). Mp: 149.0–151.1 °C. IR: 3069, 2304, 1591, 1560, 1314, 1181, 1121, 1034, 682 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (d, J = 2.4 Hz, 1H), 8.96 (dd, J = 2.4, 8.9 Hz, 1H), 8.39 (d, J = 8.9 Hz, 1H), 7.48–7.44 (m, 2H), 7.13–7.08 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 145.4, 144.0, 137.8, 137.7, 134.8, 132.8 (q, J = 6.2 Hz), 128.7 (q, J = 33.1 Hz), 128.1, 125.5, 121.0 (q, J = 273.5 Hz), 116.7, 20.8. HRMS (ESI+): calcd for $C_7H_3ClF_3N_3^+$ $[M]^+$ *m/z* 206.9931; found: 206.9931.

*3-Chloro-4-cianobenzenediazonium tosylate (**2d**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 4-amino-2-chlorobenzonitrile (**1d**, 152

mg, 1.00 mmol) and *tert*-butyl nitrite (356 µL, 3.00 mmol). The product was obtained as a white solid (278 mg, 0.83 mmol, 83%). Mp: 130.0–133.3 °C. IR: 3071, 2309, 1453, 1397, 1201, 1032, 818, 677 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (d, J = 2.0 Hz, 1H), 8.82 (dd, J = 2.0, 8.7 Hz, 1H), 8.54 (d, J = 8.7 Hz, 1H), 7.47–7.43 (m, 2H), 7.13–7.08 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 145.4, 137.8, 136.9, 136.6, 132.5, 131.5, 128.1, 125.5, 122.8, 121.9, 114.1, 20.8. HRMS (ESI+): calcd for $C_7H_3N_3Cl^+$ $[M]^+$ *m/z* 164.001; found: 164.0002.

*3-Nitrobenzenediazonium tosylate (**2e**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 3-nitroaniline (**1e**, 138 mg, 1.00 mmol) and *tert*-butyl nitrite (118.8 µL, 1.00 mmol). Crude product was recrystallized from acetone (beige solid, 175 mg, 0.64 mmol, 64%). The data were in agreement with those from the literature [26]. Mp: 137.4–138.0 °C (lit. [26] 134 °C). IR: 3080, 2306, 1597, 1535, 1349, 1191, 1119, 815, 683 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (dd, J = 2.1, 2.3 Hz, 1H), 9.04 (ddd, J = 1.0, 2.1, 8.2 Hz, 1H), 8.96 (ddd, J = 1.0, 2.3, 8.4 Hz, 1H), 8.22 (dd, J = 8.2, 8.4 Hz, 1H), 7.47–7.44 (m, 2H), 7.13–7.08 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 147.6, 145.4, 138.0, 137.8, 135.0, 133.7, 128.2, 128.1, 125.5, 118.3, 20.9. HRMS (ESI+): calcd for $C_6H_4N_3O_2^+$ $[M]^+$ *m/z* 150.0298; found: 150.0297.

*4-Nitrobenzenediazonium tosylate (**2f**):* Following the general procedure employing *p*-toluenesulfonic acid (438 mg, 2.30 mmol), 4-nitroaniline (**1f**, 138 mg, 1.00 mmol) and *tert*-butyl nitrite (118.8 µL, 1.00 mmol). Crude product was recrystallized from acetone (beige solid, 144 mg, 0.45 mmol, 45%). The data were in agreement with those from the literature [26]. Mp: 132.4–133.9 °C (lit. [26] 132 °C). IR: 3105, 2306, 1615, 1541, 1347, 1223, 1169, 1119, 822, 682 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96–8.92 (m, 2H), 8.71–8.67 (m, 2H), 7.48–7.45 (m,

2H), 7.12–7.08 (m, 2H), 2.28 (s, 3H). HRMS (ESI+): calcd for $C_6H_4N_3O_2^+$ $[M]^+$ *m/z* 150.0298; found: 150.0302.

*2-Bromo-5-nitrobenzenediazonium tosylate (**2g**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 2-bromo-5-nitroaniline (**1g**, 217 mg, 1.00 mmol) and *tert*-butyl nitrite (118.8 µL, 1.00 mmol). The product was obtained as pale yellow solid (313 mg, 0.78 mmol, 78%). Mp: 140.8–142.0 °C. IR: 3094, 2302, 1593, 1580, 1530, 1347, 1215, 1192, 1036, 680 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 8.98 (d, J = 3.2 Hz, 1H), 8.05 (dd, J = 3.2, 10.2 Hz, 1H), 7.49–7.45 (m, 2H), 7.13–7.09 (m, 2H), 6.59 (d, J = 10.2 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.9, 145.0, 138.2, 132.6, 132.2, 130.0, 128.3, 125.6, 124.2, 91.0, 20.9. HRMS (ESI+): calcd for $C_6H_3BrN_3O_2^+$ $[M]^+$ *m/z* 227.9403; found: 227.94.

*4-Nitro-2-(trifluoromethyl)benzenediazonium tosylate (**2h**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 4-nitro-2-(trifluoromethyl)aniline (**1h**, 206 mg, 1.00 mmol) and *tert*-butyl nitrite (118.8 µL, 1.00 mmol). The product was obtained as a yellow solid (289 mg, 0.74 mmol, 74%). Mp: 134.9–136.0 °C. IR: 3099, 3001, 2309, 1618, 1542, 1353, 1162, 796 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 9.35 (d, J = 9.0 Hz, 1H), 9.13 (d, J = 2.3 Hz, 1H), 9.04 (dd, J = 2.3, 9.0 Hz, 1H), 7.47–7.44 (m, 2H), 7.12–7.08 (m, 2H), 2.28 (s, 3H). ^{13}C NMR spectrum of compound **2h** could not be recorded due to its rapid decomposition in DMSO-d_6 solution. HRMS (ESI+): calcd for $C_7H_3F_3N_3O_2^+$ $[M]^+$ *m/z* 218.0172; found: 218.0166.

*2-Cyano-4-nitrobenzenediazonium tosylate (**2i**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 2-amino-5-nitrobenzonitrile (**1i**, 163 mg, 1.00 mmol) and *tert*-butyl nitrite (356 µL, 3.00 mmol). The product was obtained as a

yellow solid (152 mg, 0.44 mmol, 44%). Mp: 128.6–129.9 °C. IR: 3104, 3060, 2312, 1597, 1348, 1219, 1192, 1119, 1036, 1011, 896, 821, 799, 739, 681 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (d, J = 2.4 Hz, 1H), 8.86 (dd, J = 2.4, 8.9 Hz, 1H), 8.63 (d, J = 8.9 Hz, 1H), 7.49–7.44 (m, 2H), 7.13–7.09 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 151.3, 145.5, 137.9, 137.8, 131.8, 131.2, 128.9, 128.1, 125.5, 113.3, 113.0, 20.8. HRMS spectrum of compound **2i** could not be obtained due to its decomposition under the applied condition.

*4-(Trifluoromethoxy)benzenediazonium tosylate (**2j**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 4-(trifluoromethoxy)aniline (**1j**, 135 µL, 1.00 mmol) and *tert*-butyl nitrite (356 µL, 3.00 mmol). The product was obtained as a white solid (323 mg, 0.90 mmol, 90%). Mp: 147.3–148.1 °C. IR: 3052, 2297, 1578, 1479, 1314, 1246, 1208, 1172, 1120, 1092, 1034, 1010, 927, 848, 815, 701, 681 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88–8.84 (m, 2H), 8.00–7.97 (m, 2H), 7.48–7.45 (m, 2H), 7.12–7.09 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.8 (q, J = 1.9 Hz), 145.6, 137.7, 136.3, 128.1, 125.5, 122.2, 119.5 (q, J = 261.6 Hz), 114.2, 20.8. HRMS (ESI+): calcd for $C_7H_4F_3N_2O^+$ $[M]^+$ *m/z* 189.027; found 189.0275.

*2-Chloro-4-nitrobenzenediazonium tosylate (**2k**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 2-chloro-4-nitroaniline (**1k**, 176 mg, 1.00 mmol) and *tert*-butyl nitrite (356 µL, 3.00 mmol). The reaction mixture was stirred for 1 h. The product was obtained as a yellow solid (210 mg, 0.59 mmol, 59%). Mp: 143.5–145.2 °C. IR: 3088, 2316, 1542, 1344, 1302, 1193, 1118, 1035, 785, 680 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.13 (d, J = 9.1 Hz, 1H), 9.00 (d, J = 2.3 Hz, 1H), 8.67 (dd, J = 2.3, 9.1 Hz, 1H), 7.49–7.43 (m, 2H), 7.13–7.07 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 153.4, 145.4, 137.8,

136.8, 136.0, 128.1, 127.0, 125.5, 124.7, 122.60, 20.8. HRMS (ESI+): calcd for $C_6H_3ClN_3O_2^+$ $[M]^+$ *m/z* 183.9919; found 183.9918.

*2-Benzoyl-4-chlorobenzenediazonium tosylate (**2l**):* Following the general procedure employing *p*-toluenesulfonic acid (389 mg, 2.00 mmol), (2-amino-5-chlorophenyl)(phenyl)methanone (**1l**, 230 mg, 1.00 mmol) and *tert*-butyl nitrite (712 µL, 6.00 mmol). The reaction mixture was stirred for 24 h. The solvent was evaporated under reduced pressure. The product was obtained as brown oil (355 mg, 0.86 mmol, 86%). IR: 3088, 2278, 1665, 1597, 1556, 1283, 1120, 1031, 1005, 948, 813, 735, 708, 679 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.03 (d, J = 8.8 Hz, 1H), 8.39 (dd, J = 1.9, 8.8 Hz, 1H), 8.23–8.20 (m, 1H), 7.93–7.89 (m, 2H), 7.85–7.80 (m, 1H), 7.69–7.64 (m, 2H), 7.49–7.44 (m, 2H), 7.13–7.09 (m, 2H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 188.8, 145.9, 145.5, 138.9, 137.8, 137.2, 134.8, 134.2, 133.7, 133.6, 130.9, 129.0, 128.2, 125.5, 114.1, 20.8. HRMS (ESI+): calcd for $C_{13}H_8ClN_2O^+$ $[M]^+$ *m/z* 243.032; found 243.0318.

*6-Methoxypyridine-3-diazonium tosylate (**2m**):* Following the general procedure employing *p*-toluenesulfonic acid (190 mg, 1.00 mmol), 3-amino-6-methoxypyridine (**1m**, 125 mg, 1.00 mmol) and *tert*-butyl nitrite (356 µL, 3.00 mmol). The product was obtained as a purple solid (266 mg, 0.86 mmol, 86%). Mp: 147.9–148.9 °C. IR: 3104, 2276, 1580, 1483, 1397, 121, 1197, 1002, 815, 679 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 9.56 (d, J = 2.6 Hz, 1H), 8.77 (dd, J = 2.6, 9.3 Hz, 1H), 7.48–7.45 (m, 2H), 7.39 (d, J = 9.3 Hz, 1H), 7.13–7.09 (m, 2H), 4.13 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.7, 157.1, 145.5, 141.6, 137.7, 128.1, 125.5, 113.4, 105.0, 56.3, 20.8. HRMS (ESI+): calcd for $C_6H_6N_3O^+$ $[M]^+$ *m/z* 136.0505; found: 136.0509.

The synthesis of product **2m** was also conducted on 4 mmol scale following the general procedure, employing *p*-toluenesulfonic acid monohydrate (760 mg, 4.00 mmol), ethyl acetate (30 mL), 6-methoxypyridine-3-amine (**1m**, 498 mg, 4.00 mmol) and *tert*-butyl nitrite (1425 µL, 12.00 mmol) to give diazonium tosylate **2m** (1.0525 g, 3.42 mmol, 85%).

*Benzotriazolium tosylate (**2n'**):* Following the general procedure employing *p*-toluenesulfonic acid (380 mg, 2.00 mmol), benzene-1,2-diamine (**1n**, 108 mg, 1.00 mmol) and *tert*-butyl nitrite (356 µL, 3.00 mmol). The product was obtained as a white solid (212 mg, 0.73 mmol, 73%). Mp: 143.3–145.0 °C. IR: 1898, 1614, 1223, 1149, 1117, 1007, 822, 753 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93–7.89 (m, 2H), 7.49–7.45 (m, 2H), 7.45–7.43 (m, 2H), 7.13–7.09 (m, 2H), 4.16 (brs, 2H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 144.9, 138.7^{Btz}, 138.3, 128.3, 125.6, 125.5^{Btz}, 115.0^{Btz}, 20.9. Literature data for benzotriazole: ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 126.0, 114.9 [31]. HRMS (ESI+): calcd for $C_6H_6N_3^+$ $[M]^+$ *m/z* 120.0556; found: 120.0561.

*2.3. General procedure for the synthesis of azo compounds **3b** and **3j**.*

In a round bottomed flask equipped with a magnetic stirrer, 2-naphthol (1.1 eq) was dissolved in water (1 mL/1 mmol). pH of the reaction mixture was adjusted to 10–11 by using 10 wt % sodium hydroxide solution and cooled to 0–5 °C. Diazonium salt **2** (1 eq) was added portionwise within ca. 20 min, maintaining pH at 10–11. The reaction mixture was stirred for 30 min and the resulting pure dye **3** was collected by filtration, washed with water, and air dried.

*1-((3,4-Dichlorophenyl)diazenyl)naphthalen-2-ol (**3b**):* Following the general procedure employing 2-naphthol (48 mg, 0.33 mmol) and 3,4-dichlorobenzenediazonium tosylate (**2b**, 104 mg, 0.30 mmol). The product was obtained as a red solid (68 mg, 0.21 mmol, 73%). Mp: 139.0–

139.9 °C. IR: 1622, 1559, 1501, 1452, 1369, 1242, 1205, 1152, 1123, 1022, 986, 822, 753 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 15.82 (brs, 1H), 8.41 (d, J = 8.1 Hz, 1H), 7.78–7.71 (m, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.59–7.49 (m, 2H), 7.48–7.35 (m, 3H), 6.78 (d, J = 9.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 144.4, 140.9, 133.9, 133.2, 131.2, 131.0, 130.6, 129.2, 128.8, 128.3, 126.4, 124.6, 121.9, 119.6, 117.9. HRMS (ESI+): calcd for $C_{16}H_{11}Cl_2N_2O^+$ $[M + H]^+$ *m/z* 317.0243; found 317.0243.

*1-((4-(Trifluoromethoxy)phenyl)diazenyl)naphthalen-2-ol (**3j**):* Following the general procedure employing 2-naphthol (104 mg, 0.70 mmol) and 4-(trifluoromethoxy)benzenediazonium tosylate (**2j**, 231 mg, 0.64 mmol). The product was obtained as a red solid (185 mg, 0.56 mmol, 87%). Mp: 95.0–96.2 °C. IR: 3067, 1622, 1451, 1261, 1208, 1159, 1146, 1098, 986, 833, 753, 651 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 15.98 (brs, 1H), 8.50 (d, J = 8.5 Hz, 1H), 7.73–7.68 (m, 3H), 7.58 (d, J = 7.9 Hz, 1H), 7.56–7.52 (m, 1H), 7.42–7.37 (m, 1H), 7.31 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 9.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 148.0, 143. 8, 140.4, 133.5, 130.4, 129.1, 128.8, 128.3, 126.1, 124.5, 122.3, 121.8, 120.1 (q, J = 258.2 Hz), 119.9. ^{19}F NMR (471 MHz, $CDCl_3$) δ –57.92. HRMS (ESI+): calcd for $C_{16}H_{11}Cl_2N_2O^+$ $[M + H]^+$ *m/z* 333.0845, found 333.0847.

*2.4. General procedure for the synthesis of azo compounds **4b**,**i**,**j**,**m**.*

In a round bottomed flask equipped with a magnetic stirrer, *N*-ethyl-*N*-(2-hydroxyethyl)aniline (1 eq) was dissolved in acetic acid (8 mL/1 mmol), to which diazonium tosylate (1 eq) was added portionwise at room temperature. The reaction mixture was stirred for 15 min and the product was isolated by extraction into dichloromethane (3 × 15 mL). The combined organic layers were washed with saturated aqueous solution of sodium bicarbonate,

dried over anhydrous sodium sulphate, and the solvent was removed by rotary evaporation. Crude products **4b**,**i**,**j**,**m** were purified by radial chromatography on silica gel with petroleum ether/ethyl acetate (2:1 *v/v*).

*2-((4-((3,4-Dichlorophenyl)diazenyl)phenyl)(ethyl)amino)ethan-1-ol (**4b**):* Following the general procedure employing *N*-ethyl-*N*-(2-hydroxyethyl)aniline (66 mg, 0.40 mmol) and 3,4-dichlorobenzenediazonium tosylate (**2b**, 138 mg, 0.40 mmol). The product was obtained as an orange oil (123 mg, 0.36 mmol, 92%). Mp: 107.3–108 °C. IR: 2980, 2191, 2172, 2005, 1593, 1568, 1508, 1487, 1394, 1319, 1246, 1137, 1071, 1020, 815, 612 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 2.2 Hz, 1H), 7.85–7.80 (m, 2H), 7.69 (dd, J = 2.2, 8.5 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 6.80–6.75 (m, 2H), 3.86 (q, J = 5.8 Hz, 3H), 3.58 (t, J = 5.8 Hz, 2H), 3.52 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 151.2, 143.4, 133.3, 132.8, 130.8, 125.8, 123.2, 122.4, 111.6, 52.5, 46.0, 31.1, 12.2. HRMS (ESI+): calcd for $C_{16}H_{18}Cl_2N_3O^+$ $[M + H]^+$ *m/z* 338.0821; found 338.0819.

*2-((4-(Ethyl(2-hydroxyethyl)amino)phenyl)diazenyl)-5-nitrobenzonitrile (**4i**):* Following the general procedure employing *N*-ethyl-*N*-(2-hydroxyethyl)aniline (23 mg, 0.14 mmol) and 4-(trifluoromethoxy)benzenediazonium tosylate (**2i**, 49 mg, 0.14 mmol). The product was obtained as a dark purple solid (41 mg, 0.12 mmol, 87%). Mp: 165.5–166.5 °C. IR: 3538, 2917, 2228, 1595, 1575, 1513, 1322, 1304, 1200, 1113, 1071, 905, 821, 751, 729 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 2.5 Hz, 1H), 8.39 (dd, J = 2.5, 9.1 Hz, 1H), 7.97–7.93 (m, 3H), 6.82–6.78 (m, 2H), 3.92 (q, J = 5.7 Hz, 2H), 3.65 (t, J = 5.7 Hz, 2H), 3.61 (q, J = 7.1 Hz, 2H), 1.77–1.72 (m, OH), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 153.2, 146.3, 144.3, 129.2, 128.3, 127.9, 117.9, 115.8, 112.1, 111.9, 60.4, 52.6, 46.4, 12.3. HRMS (ESI+): calcd for $C_{17}H_{18}N_5O_3^+$ $[M + H]^+$ *m/z* 340.1404, found 340.1405.

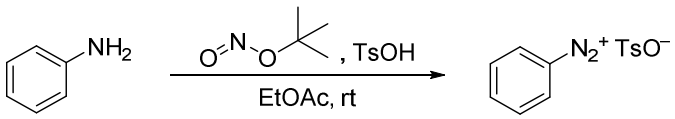
313 *2-(Ethyl(4-((4-(trifluoromethoxy)phenyl)diazenyl)phenyl)amino)ethan-1-ol* ***(4j)****:*
314 Following the general procedure employing *N*-ethyl-*N*-(2-hydroxyethyl)aniline (55 mg, 0.33
315 mmol) and 4-(trifluoromethoxy)benzenediazonium tosylate (**2j**, 117 mg, 0.33 mmol). The
316 product was obtained as a red solid (94 mg, 0.27 mmol, 81%). Mp: 83.3–84.5 °C. IR: 3252,
317 2988, 1600, 1513, 1396, 1213, 1152, 1129, 1057, 849, 818, 666 cm^{-1}. ^{1}H NMR (500 MHz,
318 $CDCl_3$) δ 7.88–7.83 (m, 4H), 7.33–7.29 (m, 2H), 6.82–6.78 (m, 2H), 3.87 (q, J = 5.8 Hz, 2H),
319 3.59 (t, J = 5.8 Hz, 2H), 3.53 (q, J = 7.1 Hz, 2H), 1.73–1.69 (m, OH), 1.23 (t, J = 7.1 Hz, 3H).
320 ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.6, 150.9, 149.8 (q, J = 1.9 Hz), 143.6, 125.5, 123.6, 121.5,
321 120.0 (q, J = 258.5 Hz), 111.7, 52.5, 46.0, 31.1, 12.2. ^{19}F NMR (471 MHz, $CDCl_3$) δ –57.76.
322 HRMS (ESI+): calcd for $C_{17}H_{18}F_3N_3O_2^+$ $[M + H]^+$ *m/z* 354.1424; found 354.1424.
323 *2-(Ethyl(4-((6-methoxypyridin-3-yl)diazenyl)phenyl)amino)ethan-1-ol* ***(4m)****:* Following
324 the general procedure employing *N*-ethyl-*N*-(2-hydroxyethyl)aniline (38 mg, 0.23 mmol) and 6-
325 methoxypyridine-3-diazonium tosylate (**2m**, 71 mg, 0.23 mmol). The product was obtained as an
326 orange solid (58 mg, 0.19 mmol, 84%). Mp: 107.3–108 °C. IR: 3362, 2968, 2871, 1709, 1593,
327 1558, 1511, 1442, 1395, 1346, 1310, 1231, 1182, 1141, 1112, 1042, 881, 818, 668 cm^{-1}. ^{1}H
328 NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 2.6 Hz, 1H), 8.07 (dd, J = 2.6, 8.9 Hz, 1H), 7.83–7.78
329 (m, 2H), 6.80 (d, J = 8.9 Hz, 1H), 6.79–6.75 (m, 2H), 4.01 (s, 3H), 3.85 (q, J = 5.8 Hz, 2H), 3.57
330 (t, J = 5.8 Hz, 2H), 3.51 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz,
331 $CDCl_3$) δ 164.8, 150.5, 146.2, 144.5, 143.7, 128.7, 125.1, 111.7, 111.6, 54.1, 52.5, 45.9, 31.1,
332 12.2. HRMS (ESI+): calcd for $C_{16}H_{21}N_4O_2^+$ $[M + H]^+$ *m/z* 301.1659; found 301.1666.
333
334 **3. Results and discussion**
335 *3.1. Synthesis of diazonium salts*

Herein, we report an effective method for the synthesis of stable diazonium salts in the presence of *tert*-butyl nitrite and *p*-toluensulfonic acid as a source of mild acidic conditions at room temperature in ethyl acetate. Solid diazonium salts were isolated from the reaction mixture by simple filtration in pure form.

The reaction between aniline, *p*-toluenesulfonic acid and *tert*-butyl nitrite in ethyl acetate as the reaction solvent at room temperature was selected as a model reaction. Optimization of diazotization conditions was conducted with different molar ratios of aniline (**1a**), *p*-toluenesulfonic acid and *tert*-butyl nitrite. The optimal ratio was found to be 1:1:3, respectively, affording phenyldiazonium tosylate (**2a**) in 99% isolated yield (Table 1, Entry 4). Although the result is similar to that for the aniline:1,5-naphthalenesulfonic acid:*tert*-butyl nitrite (1:1:1.5) system reported by Tang [24], it is much better as in the case of aniline:polymer-supported nitrite:TsOH of Filimonov, Chi *et al.* [26], for which the optimal molar ratio was reported to range from 1:3:3 to 1:6:6. Varying the amount of ethyl acetate or prolonging the reaction time had no effect on the yield of **2a**. As judged by TLC monitoring, optimal reaction time was 15 min, although precipitate started to form immediately after the addition of *tert*-butyl nitrite into the reaction mixture. No nitrogen oxides could be observed during the process.

Table 1

The effect of TsOH and *tert*-butyl nitrite loading on diazotization of aniline (**1a**).



1a **2a**

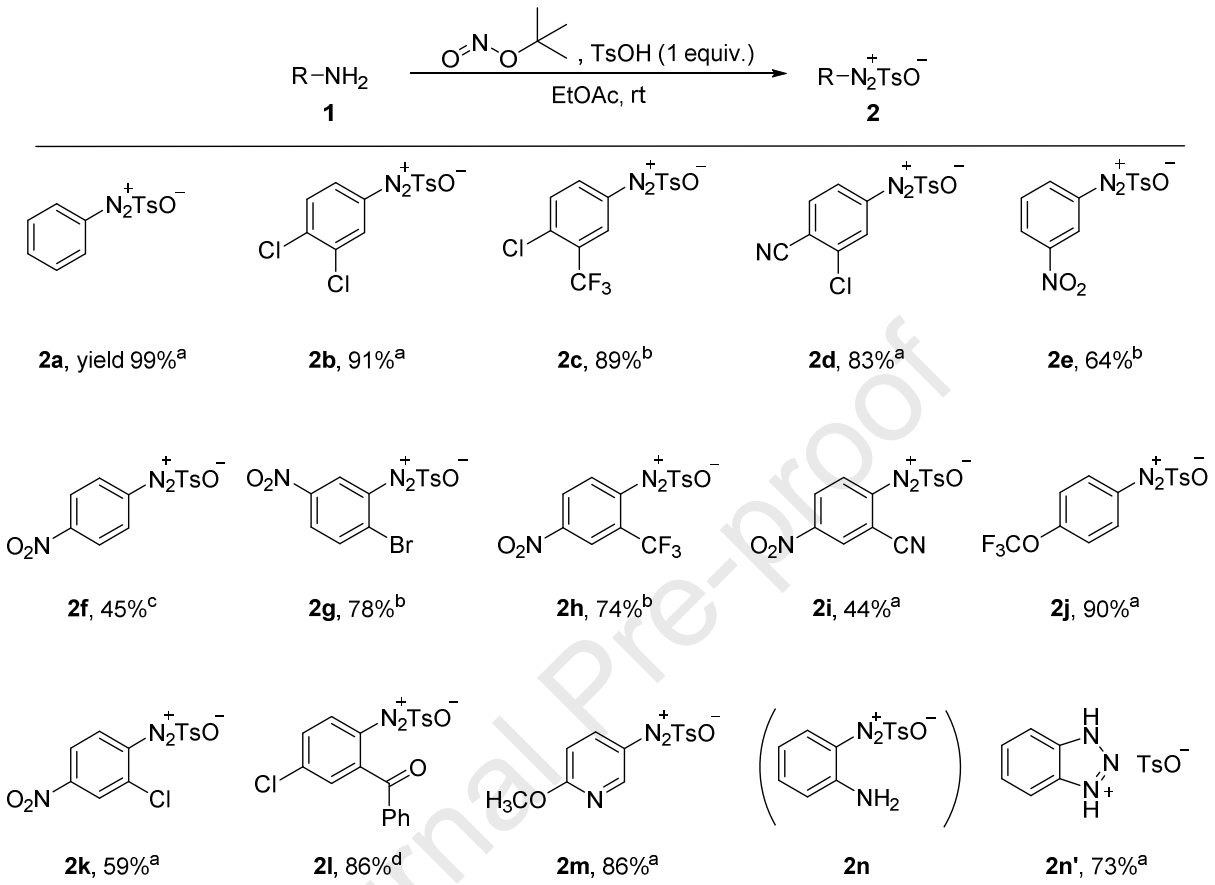
Entry	**1a** (mmol)	TsOH (eq.)	*tert*-butyl nitrite (eq.)	EtOAc (mL)	**2a**, yield (%)[a]

1	1	1	1	10	71
2	1	1	1	20	72
3	1	1	2	10	94
4	1	1	3	10	99

[a] Refers to isolated yield of pure product (average value of two independent runs).

With the optimized reaction conditions in hand, the substrate scope was investigated, and the results are collected in Fig. 2. In general, aromatic amines with electron-accepting substituents proved to be better substrates for diazotization under these reaction conditions [24]. In some cases, that of **2c**,**e**–**h**, adding only one equivalent of *tert*-butyl nitrite was enough to obtain the insoluble diazonium salt. The reactions were completed within 15 min. Longer reaction times were only required for strongly electron deficient and sparingly soluble 2-chloro-4-nitroaniline (**1k**) as well as sterically demanding (2-amino-5-chlorophenyl)(phenyl)methanone (**1l**). In case of 4-nitroaniline (**1f**) and (2-amino-5-chlorophenyl)(phenyl)methanone (**1l**) an excess (2.0–2.3 equiv.) of *p*-toluenesulfonic acid was used to achieve reasonable conversions. All products, except for **2e** and **2f**, were obtained in pure form by filtration from the reaction mixture, without further purification needed. Analytically pure products **2e** and **2f** were obtained by recrystallization. The obtained tosylates were soluble in both protic and aprotic polar solvents, which is an advantage over other types of stable diazonium salts. Interestingly, diazonium salt **2l** appeared as an oily product and was isolated from the reaction mixture by evaporation of the solvent under reduced pressure. Scalability of the protocol was tested in diazotization of aniline (**1a**), 3,4-dichloroaniline (**1b**) and 3-amino-6-methoxypyridine (**1m**) on 4 mmol scale, affording products **2a**, **2b** and **2m**, respectively, in comparable yields as on 1 mmol scale.

375



376

377 **Fig. 2.** Substrate scope, [a] 3 equiv. of *tert*-butyl nitrite were employed [b] 1 equiv. of *tert*-butyl
378 nitrite were employed [c] 2.3 eq of TsOH and 1 equiv. of *tert*-butyl nitrite were employed [d] 2 equiv.
379 of TsOH and 6 equiv. of *tert*-butyl nitrite were employed

380

381 All products were bench stable at room temperature for a long period of time. The
382 stability of the products was monitored by re-acquiring ^{1}H NMR spectra of the isolated solid
383 compounds that were stored at room temperature. Diazonium salts **2c** and **2m**, for example,
384 showed no structural changes even after a year of storage. The only exceptions were products **2a**
385 and **2k**, which decomposed within a week.

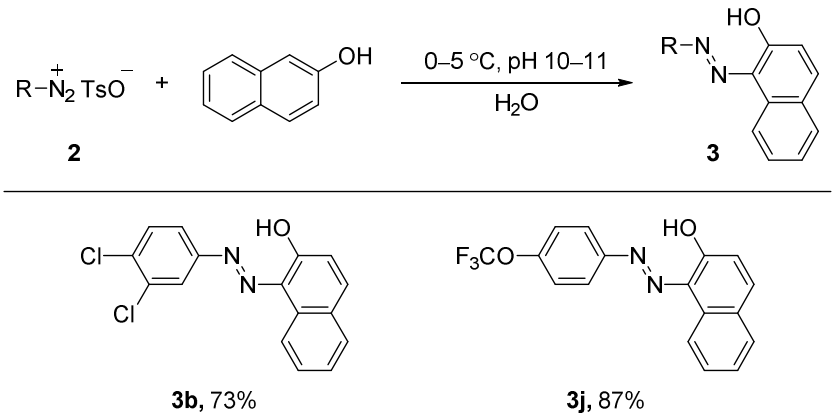
To further explore the scope, benzene-1,2-diamine (**1n**) as a representative example of *o*-phenylenediamines was let to react with *tert*-butyl nitrite in the presence of *p*-toluenesulfonic acid (Fig. 2). As expected, the transformation proceeds through intermediately formed 2-aminobenzenediazonium tosylate (**2n**) and smoothly returned benzotriazolium tosylate (**2n'**). In an unoptimized reaction, the product was obtained in pure form in 73% isolated yield (Fig. 2). The ^{1}H NMR and ^{13}C NMR spectra of the product benzotriazolium salt **2n'** recorded in DMSO-d_6 are in agreement with those for the parent benzotriazole [31]. Benzotriazoles are important entities in organic synthetic and medicinal chemistry and have been recently prepared by *tert*-butyl nitrite mediated nitrogen transfer to *o*-phenylenediamines [31]. Crystal structure of benzotriazolium tosylate has been reported [32].

3.2. Synthesis of azo compounds

*3.2.1. Synthesis of azo compounds **3***

Diazonium tosylates **2b** and **2j** were tested in the synthesis of azo dyes with 2-naphthol (Fig. 3). The reactions were conducted in alkaline aqueous solutions with pH being maintained at 10–11 to enhance the reactivity of the naphthol coupling partner. As judged by TLC analysis the reactions were complete once the coupling partners were combined. To allow for complete precipitation of the products, the reaction mixtures were stirred for additional 30 min after which crude products **3b** and **3j** were isolated by filtration in 73% and 83% yields, respectively. The crude products were NMR pure and required no additional purification. The coupling protocol and the results are comparable to those reported by Tang and co-workers [33], and superior to the traditional approach that involves diazotization under strongly acidic conditions, especially for weakly basic anilines, followed by azo coupling reaction at high pH [34].

409



410

411 **Fig. 3.** Synthesis of azo dyes **3** from selected diazonium salts **2**

412

413 *3.2.1. Synthesis of azo compounds **4***

414 In addition to 2-naphthol, coupling of diazonium tosylates was also tested with *N*-ethyl-
415 *N*-(2-hydroxyethyl)aniline to give azo compounds **4**. The interest in using this coupling partner
416 steams form the fact that the resulting rod-like products of structure **4** having a delocalized π-
417 system have the potential to label protein aggregates of different compositions formed in the
418 brain of patients suffering from neurodegenerative diseases like Alzheimer disease [35,36]. The
419 frameworks based on azo dyes like Chrysamine G, Thiazine Red, Sirius Red F3B, and Benzo
420 Scarlet 4BNS (amyloid red) are notable [37]. Furthermore, the *N*-(2-hydroxyethyl) fragment
421 enables a facile entry to radiolabeled fluorine-18 *N*-(2-[^{18}F]fluoroethyl) derivatives that can be
422 used as radiotracers to image neurodegenerative diseases [38]. Other applications in
423 optoelectronic devices and other functional materials can be envisioned [39].

424 Diazotization of *N*-ethyl-*N*-(2-hydroxyethyl)aniline was conducted with **2**(**b**,**i**,**j**,**m**) at
425 room temperature. Acetic acid was used as a reaction solvent to assure the solubility of the
426 aniline coupling partner. Products **4**, formed almost instantly after the reactants were combined,

were isolated by extraction into dichloromethane and purified by radial chromatography. This protocol is notably different to the classical diazotization where the use of strongly acidic reaction conditions largely deactivates anilines by protonation. [40].

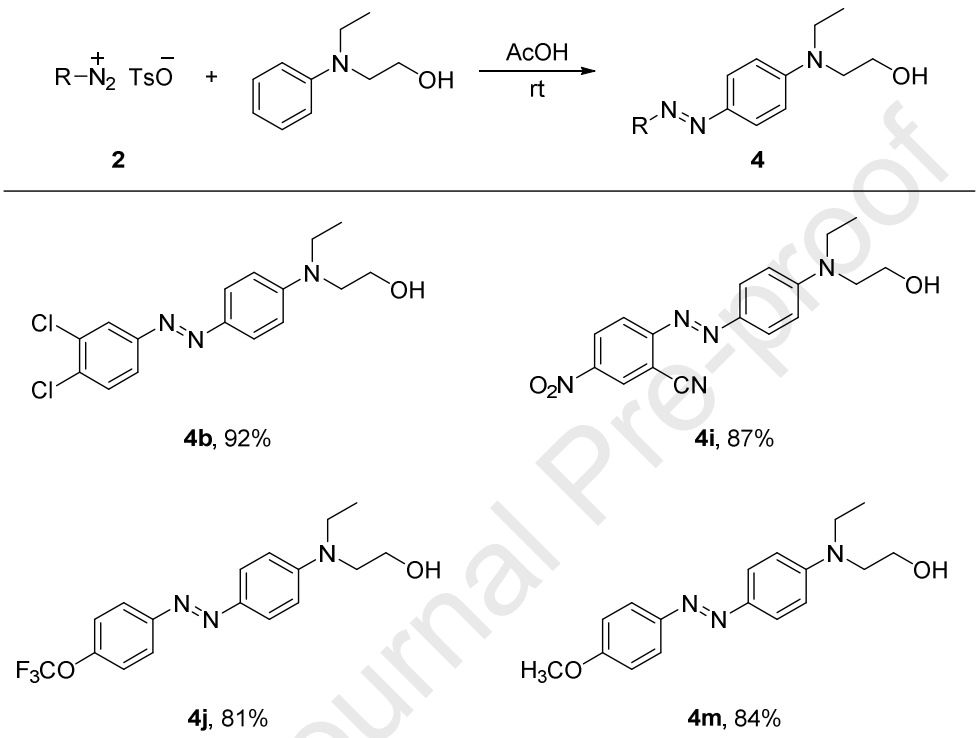


Fig. 4. Synthesis of azo dyes **4** from selected diazonium salts **2**

4. Conclusion

We have demonstrated an efficient, environmentally friendly, and simple protocol for the synthesis of stable diazonium tosylates from the appropriate aromatic amines, *p*-toluenesulfonic acid and *tert*-butyl nitrite in ethyl acetate at room temperature. The substrate scope shows that aromatic amines with electron-withdrawing substituents are more suitable substrates for diazotization under the employed reaction conditions. In most cases the products were obtained in pure form by simple evaporation of the reaction solvent and exhibited great stability over a

longer period of time. The method is applicable for the transformation of *o*-phenylenediamines benzotriazolium tosylates. Application in the synthesis of azo dyes has been demonstrated.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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It provides an easy access to diazonium tosylates.

It employs mild reaction conditions, using inexpensive reagents.

Tosylate counterion increases the stability of diazonium salt.

Diazonium tosylates readily afford azo compounds.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: