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Synthesis of alkylthio benzene derivatives via simultaneous diazotization and nucleophilic displacement

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ABSTRACT

Alkylthio benzene derivatives were effectively synthesized by simultaneous diazotization of aromatic amines and nucleophilic displacement. The method is fairly general and proceeds in moderate yields. Product yields were comparable regardless of steric hindrance of the thiol or of the functional group present in the starting material. The newly developed procedure allowed for the incorporation of a tertiary alkylthio group, which cannot be easily introduced otherwise. The products were characterized by ^{1}H NMR and ^{13}C NMR.

The formation of C-S bonds is an active research area due to their wide applicability and profound effect on the synthesis of key intermediates to biologically active molecules, as well as playing a special role in the application of organic, medicinal, and heterocyclic synthesis. [1] A special interest has been given to the introduction of C-S bonds into aryl derivatives.

Many methodologies have been developed to accomplish this task. Transition-metal coordinated and catalyzed reactions with thiols and aryl halides have proved to be one of the most popular methods. [2] The reaction of aryl bromides with cuprous mercaptides afford a wide range of alkylthio benzene derivatives, but suffer from relatively high temperatures and the synthesis of the cuprous mercaptides adds an extra step to the overall reaction.[3] Likewise, CuI and Cs_2CO_3 catalyzed reactions have been reported in the literature [4,5]. However, reaction times are prolonged and removal of the transition metal may become burdensome [6]. Grignard reagents have also been employed [6,7], but the reactive nature of the reagents calls for the integration of protection steps into the synthesis for those reactions in which the starting materials are highly functionalized. Hence, mild approaches to circumvent these problems are highly desirable. In addition, a major drawback of many of the methodologies listed is their failure to introduce tertiary alkylthio substituents. An instance in the literature involves gas phase reactions or the use of metal catalysts at high temperatures. [8]

The use of diazonium salts as a synthetic precursors has received attention due to their ease of preparation under generally mild conditions. Several papers have cited the use of arene diazonium salts as excellent precursors for the introduction of halogens, alkoxy groups, and other functional groups [9–13]. Most notably, variations in the well-known Ziegler reaction have been used in the synthesis of alkylthiobenzene derivatives. [14] A drawback to this synthesis, however, is the possible formation of diazosulfides, highly reactive and explosive species that pose a problem for the incorporation of this protocol in an industrial scale. Although advances in this synthesis has reduced the danger of this dangerous intermediate, caution is still obligatory, and the storage of diazonium salts still pose a problem as they are potentially explosive in the dry state.

Reported here is the introduction of alkylthio substituents through the *in-situ* formation and displacement of the diazonium by the nucleophilic thiol (Scheme 1) as the means of producing a viable, mild, and short one-pot reaction. This method also allowed the introduction of a tertiary alkyl-thio substituents without the need of gas phase reactions, high temperature, or the use of metal catalysts.

Preliminary results in which the alkanethiol was added after the formation of the diazonium salt was complete (Scheme 1), resulted in low yields of the substitution product. Accordingly, when the alkanethiol was added after allowing the formation of the diazonium salt, a deep colored precipitate was obtained, suggesting the formation of an azo dye. This was observed especially when activated aniline derivatives were used (i.e. R = OCH_3). In the latter case, no substitution product was obtained. Entry $3a_1$ from Table 1 shows the percent yield of the reaction between the diazonium salt of *p*-nitroaniline with 1-hexanethiol. The alkanethiol was added after allowing the diazonium salt to age for 30

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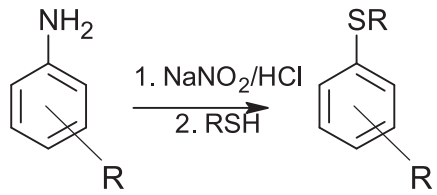
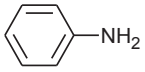
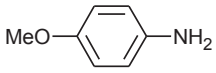
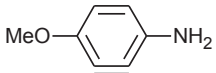
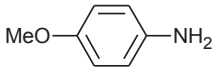
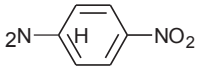
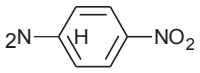
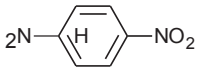
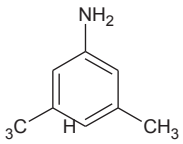


Scheme 1. Diazotization followed by nucleophilic displacement.

Table 1
Simultaneous diazotization and nucleophilic displacement.

Product	Substrate	R-SH	Isolated Yield (%)
1a		1-hexanethiol	77
2a		1-hexanethiol	50
2b		2-ethylhexanethiol	53
2c		*tert*-butylthiol	49
$3a_1$		1-hexanethiol (added after diazonium salt is aged 30 min)	12
$3a_2$		1-hexanethiol (added after addition of $NaNO_2$)	30
$3a_3$		1-hexanethiol	62
4a		1-hexanethiol	63

min, resulting in an isolated yield of 12 %. When the alkane thiol was added immediately after the addition of sodium nitrite (entry $3a_2$), the reaction yield increased to 30 %.

When an aqueous solution of sodium nitrite and alkanethiol were added simultaneously to a cooled solution of aniline and concentrated HCl in acetonitrile, vigorous gas evolution was observed. This was likely due the displacement of nitrogen gas. ^{1}H NMR confirmed the formation of the aromatic alkylthio derivative. Hence, to increase the reaction yield, we proposed simultaneous addition of the diazotization reagent ($NaNO_2$) and the nucleophile alkanethiol (R-SH) to solutions of the aniline derivative and concentrated HCl in acetonitrile. Thus, diazotization and nucleophilic displacement are expected to occur simultaneously (Scheme 2).

Preliminary characterization of the byproducts suggested the formation of disulfide bonds (triplet at ca. 2.65 ppm). Degassing the solvents prior to the reaction proved to be an effective method in the prevention of the oxidation of the sulfhydryl groups. Degassing was

Scheme 2. Simultaneous diazotization and nucleophilic displacement.

achieved by alternating cycles of vacuum and nitrogen. This step, in conjunction to the simultaneous addition of the reagents, led to much higher yields than the initial experiments.

Table 1 shows the results from the simultaneous diazotization and nucleophilic displacement on a variety of aniline derivatives. Except for entries $3a_1$ and $3a_2$, all reactions were conducted using degassed solvents. The mechanism of action is thought to be aromatic nucleophilic substitution [15], where electron withdrawing groups are favored para or ortho to the leaving group. This proposed mechanism suggests that electron donating groups at these positions make the reaction unfavorable. However, we observed that the yields were comparable regardless of electron donating or withdrawing substituents on the aromatic ring. Reactions were unaffected by the presence of a methoxy group para to the site of alkylation. Normally, substitution does not happen due to activation by the methoxy group, leading to self-coupling and the formation of a dye, which were not a byproduct of the reactions. The reaction yields, on the other hand, varied depending on the bulkiness of the thiol. Higher yields were obtained from primary thiols, with the lowest being those from the tertiary alkanethiol. The percent yield, however, was similar compared to reports from the literature [8], with the advantage of milder, shorter, and relatively facile reaction conditions. Reaction times were generally short (<30 min) and were easily monitored by the evolution of N_2 gas as well as color change within the reaction mixture and TLC.

In conclusion, we developed a new synthetic route for the introduction of alkylthio substituents through the diazotization and nucleophilic displacement of the arene diazonium salts without the need for transition metal catalysts and relatively mild and safe conditions. Further mechanistic studies are needed as well as a thorough characterization of by-products in order to obtain a better understanding of the reaction pathway.

Typical Reaction Procedure: All chemicals were obtained from Sigma Aldrich unless otherwise noted and used without further purification. All solvents were obtained from Fisher Scientific and were degassed prior to use. ^{1}H NMR and ^{13}C NMR spectra were taken using a FT-NMR 600 MHz Bruker Ultrashield plus NMR. Water and acetonitrile were degassed by alternating cycles of nitrogen and vacuum, prior to its use in the simultaneous diazotization and nucleophilic displacement reactions.

Diazotization followed by nucleophilic displacement. 1.32 g of p-nitroaniline (9.77 mmole) were added to a round-bottom flask (equipped with a stir bar) containing 15 mL of acetonitrile and 1.2 mL of concentrated hydrochloric acid. The solution was stirred while immersed in a water-ice bath. 0.94 g of sodium nitrite (13.6 mmole) were added to the round-bottom flask. The reaction mixture was aged for 30 min, after which 1.41 g of 1-hexanethiol (11.9 mmole) were added. The ice-water bath was removed, and the solution was allowed to reach room temperature.

Simultaneous diazotization and nucleophilic displacement. 10 mmol of the starting material were added to a round bottom flask equipped with a stir bar loaded with 15 mL of acetonitrile and 1.2 mL of hydrochloric acid. The reaction vessel was cooled in a water-ice-bath. 14 mmol of sodium nitrite were dissolved in 3 mL of water and loaded into a syringe. 12 mmole of the alkanethiol were dissolved in acetonitrile. The volume of the solution was adjusted to that of the sodium nitrite solution. Both syringes were placed on a syringe pump and connected to Teflon tubing leading into the reaction vessel. A delivery rate of 10 mL/hr was used to pump both solutions into the reaction vessel. After the reagents were added, the reaction was allowed to cool to room temperature and allowed to age for approximately twenty to thirty minutes.

The resulting mother liquor was partitioned between diethyl ether and water, and the resulting organic layer was concentrated by vacuum to yield a crude oil. Further purification was obtained through column chromatography, and the product was characterized through proton and carbon NMR to confirm the structure of the products.

1a: 1-(hexylthio)-benzene

The general procedure was followed. Purification through column chromatography afforded a liquid. Yield = 77% ^{1}H NMR (600 MHz, CDCl3): δ = 7.31 (d, 2H), 7.26 (t, 2H), 7.14 (d, 1H), 2.90 (t, 2H), 1.63 (m, 2H), 1.42 (m, 2H), 1.29 (m, 4H), 0.89 (t, 3H) ppm. ^{13}C NMR (600 MHz, CDCl3): δ = 137.10, 128.84, 128.79, 125.60, 33.59, 31.38, 29.13,28.53, 22.54, 14.01 ppm.

2a: 1-(hexylthio)-4-methoxybezene

The general procedure was followed. Purification through column chromatography afforded a liquid. Yield = 50.2%. ^{1}H NMR (600 MHz, CDCl3): δ = 7.33 (d, 2H), 6.83 (d, 2H), 3.79 (s, 3H), 2.81 (t, 2H), 1.57 (m, 2H), 1.38 (m, 2H), 1.28 (m, 2H), 0.87 (t, 3H) ppm. ^{13}C NMR (600 MHz, CDCl3): δ = 158.73, 132.88, 127.02, 114.49, 55.28, 35.83, 31.40, 29.35, 29.35, 31.40, 29.35, 28.41, 22.56, 14.02 ppm.

2b: 1-[(2-ethylhexyl)] thio-4-methoxybezene

The general procedure was followed. Purification through column chromatography afforded a liquid. Yield = 53.4 %. ^{1}H NMR (600 MHz, CDCl3): δ = 7.32 (d, 2H), 6.82 (d, 2H), 3.77 (s, 3H), 2.81 (d, 2H), 1.36 (m, 10*H*), 0.88 (t, 3H), 0.85 (t, 3H). ^{13}C NMR (600 MHz, CDCl3): δ = 158.59, 132.62, 127.80, 114.49, 55.29, 40.38, 39.03, 32.24, 28.76, 25.44, 22.98, 14.09, 10.72 ppm.

2c: 1-[(1,1-dimethylethyl)thio] -4-methoxybenzne

The general procedure was followed. Purification through column chromatography afforded a liquid. Yield = 49.3 %. ^{1}H NMR (600 MHz, CDCl3): δ = 7.56 (d, 2H), 6.92 (d, 2H), 3.84 (s, 3H), 1.62 (s, 9H) ppm. ^{13}C NMR (600 MHz, CDCl3): δ = 138.84, 123.61, 122.79, 122.79, 113.95, 55.21, 45.42, 30.75 ppm.

3a: 1-(hexylthio)-4-nitrobezene

The general procedure was followed. Purification through column chromatography afforded a liquid. Yield = 60.3%. ^{1}H NMR (600 MHz, CDCl3): δ = 8.09 (d, 2H), 7.34 (d, 2H), 3.02 (d, 2H), 1.71 (m, 2H), 1.48 (m, 2H), 1.33 (m, 4H), 0.90 (t, 3H), ppm. ^{13}C NMR (600 MHz, CDCl3): δ = 148.23, 144.84, 125.98, 123.90, 31.97, 31.30, 28.56, 28.47, 22.51, 13.99 ppm

4a: 1-(hexylthio)-3,5-dimethylbenzene

The general procedure was followed. Purification through column chromatography afforded a liquid. Yield = 62.9%. ^{1}H NMR (600 MHz, CDCl3): δ = 6.93 (s, 2H), 6.77 (s, 1H), 2.87 (t, 2H), 2.30 (m, 6H), 1.64 (m, 2H), 1.35 (m, 6H), 0.90 (t, 3H), ppm. ^{13}C NMR (600 MHz, CDCl3): δ = 138.34, 136.61, 127.52, 126.48, 39.23, 33.52, 31.47, 31.39, 29.22, 29.17, 28.56, 28.23, 22.56, 21.22, 14.03 ppm.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jose J. Gutierrez reports financial support was provided by National Science Foundation. Jose J. Gutierrez reports financial support was provided by Welch Foundation.

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