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Alkylation of SH-Heterocycles with Diethyl Phosphite Using Tetrachloroethylene as an Efficient Solvent

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ABSTRACT: *Treatment of mercapto-heterocyclic compounds with diethyl phosphite in the presence of 4-dimethylaminopyridine (DMAP) in tetrachloroethylene has given the S-ethylated product in good yields and high chemoselectivity. This procedure is compatible with a wide range of SH-compounds such as 1,3,4-oxadiazole-2-thiol, 1,3,4-thiadiazole-2-thiol, benzo[d]thiazole-2-thiol, and substituted benzenethiol.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:653–658, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20729

INTRODUCTION

Dialkyl phosphites, as a kind of useful phosphorus-containing reagents, are widely applied to the synthesis of organophosphonate derivatives, which are an important class of biologically active compounds [1]. A large number of useful transformations have been achieved during the past decades, in which dialkyl phosphites were used as standard nucleophilic species for the construction of C—P bonds, in which various compounds can act as the acceptor, such as imines (ketimines) [2], carbonyl groups [3], α, β-unsaturated carbonyl compounds [4], nitroalkenes [5], and so on. Recently, some new catalyst systems have also been developed to fully promote the use of dialkyl phosphites in different ways (Fig. 1). Among these efficient protocols toward the use of dialkyl phosphite derivatives, cleavage of the P—H bond was inevitably involved homolytic cleavage [6] as the source of *P*-centered radicals under radical-initiated or heterolytic cleavage conditions [7]. Besides, there are few reports showing that dialkyl phosphites could also participate in the construction of C—N and C—O bonds, involving the cleavage of the C—O bond [8]. Generally, the reaction was performed at a high temperature (100–169°C) in the presence of catalytic amounts of acid. Although few publications have reported *S*-alkylation of SH compounds by trialkylphosphites [9], we have not observed any *S*-alkylation using dialkyl phosphites. This efficient approach to alkylation of nitrogen heterocycles and etherification of alcohols was largely ignored in the later decades, and

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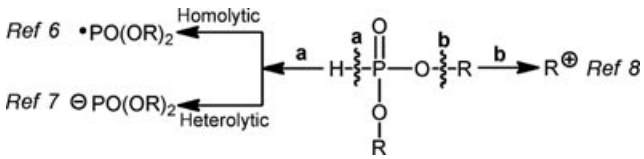


FIGURE 1 Reactions of dialkyl phosphite.

therefore the scope and limitation of dialkyl phosphites as an alternative alkylation agent is still limitedly explored.

The thioether linkage is present in numerous bioactive, natural and pharmaceutical agents. A few methods are proposed for the preparation of C—S bonds. Most of the existing methods for the synthesis of thioethers require the use of functionalized substrates such as α-halocarbonyl compounds [10], alkyl orthoformates [11], substrates that contain acidic C—H bonds [12], α, β-unsaturated carbonyl compounds [13], or allylic acetates/carbonates [14]. More recently, Robertson and Wu [15] reported that the allylic thioethers were prepared in one step by the addition of an exogenous alkoxide to the corresponding allylic phosphorothioate ester.

Considering that the skeletons of 1,3,4-thiadiazole and 1,3,4-oxadiazole are active medicinal agents for the treatment of many diseases, including tiodazosin, nesapidil, antibiotics HIV integrase inhibitors, and angiogenesis inhibitors [16], we describe here an efficient method for *S*-ethylation of 2-mercapto-1,3,4-thiadiazoles and 2-mercapto-1,3,4-oxadiazoles with diethyl phosphite, in the presence of 4-dimethylaminopyridine (DMAP) as catalyst.

RESULTS AND DISCUSSION

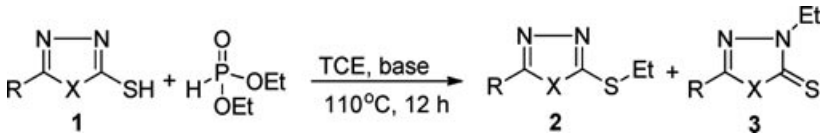
Initially, we chose the reaction of 1,3,4-thiadiazole-2-thiol **1a** with diethyl phosphite as a model reaction to optimize the reaction conditions. The results are summarized in Table 1. An extensive investigation of a range of solvents and catalysts was carried out. The reaction between **1a** and diethyl phosphite did not occur in refluxing benzene, tetrahydrofuran (THF), and ethanol in the presence of pyridine. Interestingly, when the reaction of **1a** with diethyl phosphite was carried out in the presence of pyridine in tetrachloroethylene (TCE), the reaction was cleanly completed within 12 h and led to the selective preparation of 2-(ethylthio)-1,3,4-thiadiazoles **2a** in 55% yield and formation of 3-ethyl-1,3,4-thiadiazole-2(3H)-thione **3a** in 16% yield (entry 1 in Table 1). Thus, to improve the regioselectivity of the thioethylation, we thenperformed the reaction using several different bases. When Et_3N, NaH, or K_2CO_3 was used instead of pyridine, both the product yield and the selectivity were reduced (entries 2–4, Table 1). In the presence of DMAP, however, both the yield and the selectivity of 2-(ethylthio)-1,3,4-thiadiazole (**2a**) were improved (entry 5, Table 1). Thus, when 20 mol% of DMAP was used as a catalyst, a similar reaction proceeded smoothly to produce *S*-ethylated products as major products, with high regioselectivity. On the basis of the catalyst and the reactivity, the reaction conditions shown in run 5 were the optimal conditions for the present thioethylation. Thus, we decided to use 2 equiv of diethyl phosphite in TCE at 110°C using DMAP as catalyst as the optimal reaction conditions for the preparation of *S*-ethyl products.

With these results, we then explored the scope and generality of this alkylation reaction (entries 6–12, Table 1). First, we changed the phenyl group **1a** to 2-chlorophenyl (**1b**) and 4-methylphenyl (**1c**), and the reaction occurred smoothly, affording the desired products in good yields and regioselectivities. Treatment of benzo[*d*]thiazole-2-thiol **1d** and 5-(benzofuran-2-yl)-1,3,4-oxadiazole-2-thiol **1e** with diethyl phosphite also led to the *S*-ethyl products **2d** and **2e**, with formation of *N*-ethyl products **3d** and **3e**, respectively (entries 8 and 9). Interestingly, all reactions gave *S*-ethylated products **2** as the major products.

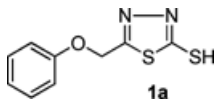
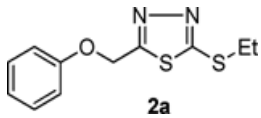
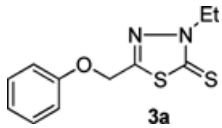
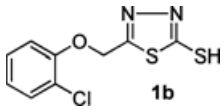
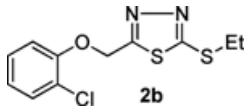
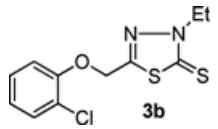
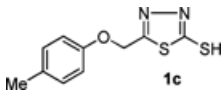
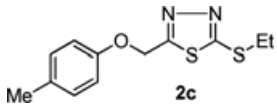
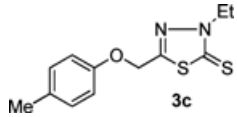
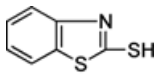
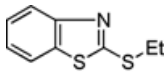
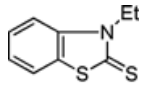
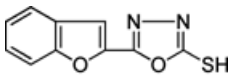
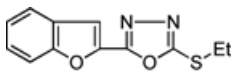
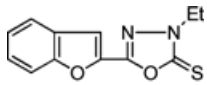
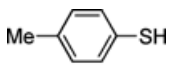
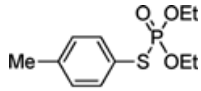
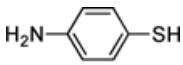
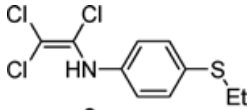
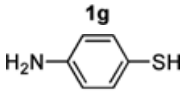
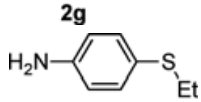
These promising results then encouraged us to investigate the possible reaction of thiophenols with diethyl phosphite. Interestingly, when 4-methylbenzenethiol (**1f**) was treated with diethyl phosphite in tetrachloroethylene at 110°C, *O*,*O*-diethyl *S*-(4-methylphenyl)phosphorothioate (**2f**) was obtained with good yield (86%; entry 10, Table 1). However, when 4-aminobenzenethiol (**1g**) was used as a substrate, 4-(ethylthio)-N-(1,2,2-trichlorovinyl)aniline (**2g**) was isolated with 76% yield (entry 11, Table 1). In this reaction, substitution occurred both on the amino and mercapto groups by attacking on tetrachloroethylene and diethyl phosphite, respectively. As expected, only the *S*-ethylated product 4-(ethylthio)aniline (**2h**) was obtained in moderate yield when the reaction was performed in toluene at 110°C (entry 12, Table 1). Efforts to widen the scope of this reagent, improvement in the synthesis and scale-up, and its continued integration into diversity-oriented synthetic protocols are underway.

According to Kornblum's rule [17], we presumed that direct alkylation of the SH group in the presence of a base would be expected; in a kinetically favored charge-controlled process, *N*-alkylation occurs and is followed by a transformation to more thermodynamically stable *S*-ethylated products.

TABLE 1 Reaction of HS-Heterocycles with Diethyl Phosphite



1 2 3

			Isolated Yield (%)	
Entry	**1**	*Base*	**2**	**3**
1	 **1a**	Py	 **2a** 55	 **3a** 16
2	**1a**	NaH	47	17
3	**1a**	Et_3N	46	20
4	**1a**	K_2CO_3	50	23
5	**1a**	DMAP	73	16
6	 **1b**	DMAP	 **2b** 76	 **3b** 10
7	 **1c**	DMAP	 **2c** 78	 **3c** 13
8	 **1d**	DMAP	 **2d** 76	 **3d** 10
9	 **1e**	DMAP	 **2e** 73	 **3e** 11
10	 **1f**	DMAP	 **2f** 86	
11[a]	 **1g**	DMAP	 **2g** 76	
12[b]	 **1g**	DMAP	 **2h** 78	

[a]Reaction was carried out in tetrachloroethylene.
[b]Reaction was carried out in toluene.

CONCLUSION

In conclusion, we have described an efficient method for the synthesis of heterocyclic thioethers starting from diethyl phosphite and SH-heterocycles. This chemistry is compatible with a wide range of heterocycles such as 1,3,4-oxadiazole, 1,3,4-thiadiazole, and benzo[*d*]thiazole. We have also demonstrated that two competing reactions have occurred, giving *S*-alkylated heterocycles as major products, and *N*-alkylated products when 1,3,4-oxadiazole-2-thiol and 1,3,4-thiadiazole-2-thiol were used. This protocol utilized diethyl phosphite as an ethylated substrate giving high yield products and avoiding the use of strong bases and highly toxic agents such as ethyl halides or diethyl sulfate.

EXPERIMENTAL

General

All reagents were obtained commercially and were used without further purification. Melting points were determined on an XT-4 electrothermal micromelting point apparatus (Beijing Electrothermal Company, Beijing, China) and were uncorrected. NMR spectra were recorded at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, on a Varian Mercury plus-400 instrument (Agilent Technologies, Inc., Santa Clara, CA) using $CDCl_3$ as a solvent and tetramethylsilane as the internal standard. Mass spectra were recorded on a TRACE DSQ instrument (Thermo Fisher Scientific, Inc.). All commercially available substrates were used as received. Thin-layer chromatography (TLC) was performed on 5 × 10 cm aluminum plates coated with silica gel 60F-254, in an appropriate solvent. 1,3,4-Thiadiazole-2-thiols and 1,3,4-oxadiazole-2-thiols were synthesized by our group [18].

General Experimental Procedure for the Reaction of 1,3,4-Oxadiazole-2-thiols with Diethyl Phosphite

To a solution of 1,3,4-thiadiazole-2-thiol (**1**) (1 mmol) and DMAP (0.2 mmol) in tetrachloroethylene (2 mL), diethyl phosphite (2 mmol) was added. After being stirred for 12 h at 110°C, the reaction mixture was concentrated under reduced pressure. Purification by chromatography on silica gel using ethyl acetate in petroleum ether (boiling point 60–90°C) gave pure samples of products **2** and **3**.

*2-(Benzyloxy)-5-(ethylthio)-1,3,4-thiadiazole (**2a**).* Yellow liquid, yield 73% (ethyl acetate/petroleum ether = 1/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–6.97 (m, 5H, H_{Ar}), 5.42 (2H, OCH_2), 3.34 (q, J = 7.6 Hz, 2H, CH_2CH_3), 1.46 (t, J = 7.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 166.6, 157.3, 129.6, 114.7, 112.0, 64.7, 28.5, 14.4. MS: m/z = 252 (M^+). Anal. calcd for $C_{11}H_{12}N_2OS_2$ (252.04): Calcd. C 52.35, H 4.79, N 11.10. Found: C 52.24, H 4.85, N 11.01.

*2-(Benzyloxy)-5-(ethylthio)-1,3,4-thiadiazole (**3a**).* Yellow solid, mp 78–80°C, yield: 16% (ethyl acetate/petroleum ether = 1/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2H, H_{Ar}), 7.06–7.03 (m, 1H, H_{Ar}), 6.97–6.94 (m, 2H, H_{Ar}), 5.13 (2H, OCH_2), 4.37 (q, J = 0.8 Hz, 2H, CH_2CH_3), 1.45 (t, J = 0.8 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.8, 157.0, 156.5, 129.7, 122.3, 114.8, 64.5, 46.3, 12.9. MS: m/z = 252 (M^+). Anal. calcd for $C_{11}H_{12}N_2OS_2$ (252.04): Calcd. C 52.35, H 4.79, N 11.10. Found: C 52.42, H 4.83, N 11.03.

*2-((2-Chlorobenzyl)oxy)-5-(ethylthio)-1,3,4-thiadiazole (**2b**).* Yellow solid, mp 64–66°C, yield 76% (ethyl acetate/petroleum ether = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 1H, H_{Ar}), 7.27–7.22 (m, 1H, H_{Ar}), 7.06–6.96 (m, 2H, H_{Ar}), 5.49 (s, 2H, OCH_2), 3.38–3.33 (m, 2H, CH_2CH_3), 1.57–1.46 (m, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 153.0, 130.6, 127.9, 122.9, 114.2, 65.8, 28.6, 14.4. MS: m/z = 286 (M^+). Anal. calcd for $C_{11}H_{11}ClN_2OS_2$ (286.00): Calcd. C 46.07, H 3.87, N 9.77. Found: C 46.16, H 3.84, N 9.81.

*5-((2-Chlorobenzyl)oxy)-3-ethyl-1,3,4-thiadiazole-2(3H)-thione (**3b**).* Yellow solid, mp 90–92°C, yield 10% (ethyl acetate/petroleum ether = 1/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.39 (m, 1H, H_{Ar}), 7.26–7.22 (m, 1H, H_{Ar}), 7.03–6.96 (m, 2H, H_{Ar}), 5.19 (2H, OCH_2), 4.36 (q, J = 7.2 Hz, 2H, CH_2CH_3), 1.43 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.0, 155.9, 152.8, 130.8, 127.8, 123.8, 123.4, 114.5, 65.7, 46.4, 12.9. MS: m/z = 286 (M^+). Anal. calcd for $C_{11}H_{11}ClN_2OS_2$ (286.00): Calcd. C 46.07, H 3.87, N 9.77. Found: C 46.18, H 3.91, N 9.70.

*2-(Ethylthio)-5-((4-methylbenzyl)oxy)-1,3,4-thiadiazole (**2c**).* Yellow solid, mp 64–66°C, yield: 78%; (ethyl acetate/petroleum ether = 1/20); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, J = 6.8 Hz, 2H, H_{Ar}), 6.87 (d, J = 6.8 Hz, 2H, H_{Ar}), 5.39 (2H, OCH_2), 3.34 (q, J = 7.2 Hz, 2H, CH_2CH_3), 2.29 (s, 3H, CH_3), 1.46 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 166.9, 155.2, 131.4, 130.1, 114.6, 64.9, 28.5, 20.4, 14.4. MS: m/z = 266 (M^+). Anal. calcd for $C_{12}H_{14}N_2OS_2$ (266.05): Calcd. C 54.11, H 5.30, N 10.52. Found: C 54.02, H 5.34, N 10.46.

*3-Ethyl-5-((4-methylbenzyl)oxy)-1,3,4-thiadiazole-2(3H)-thione (**3c**).* Yellow solid, mp 86–88°C, yield 13% (ethyl acetate/petroleum ether = 1/20); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, J = 6.4 Hz, 2H, H_{Ar}), 6.84 (d, J = 6.4 Hz, 2H, H_{Ar}), 5.10 (2H, OCH_2), 4.36 (q, J = 7.2 Hz, 2H, CH_2CH_3), 2.29 (s, 3H, CH_3), 1.43 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.8, 156.8, 155.0, 131.8, 130.1, 114.7, 64.7, 46.3, 20.4, 12.9. MS: m/z = 266 (M^+). Anal. calcd for $C_{12}H_{14}N_2OS_2$ (266.05): Calcd. C 54.11, H 5.30, N 10.52. Found: C 54.19, H 5.34, N 10.46.

*2-(Ethylthio)benzo[d]thiazole (**2d**).* Colorless liquid, yield: 76% (ethyl acetate/petroleum ether = 1/30); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.85

(m, 1H, H_{Ar}), 7.75–7.73 (m, 1H, H_{Ar}), 7.42–7.38 (m, 1H, H_{Ar}), 7.29–7.25 (m, 1H, H_{Ar}), 3.38–3.32 (m, 2H, CH_2CH_3), 1.51–1.45 (m, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 153.3, 135.1, 125.9, 124.0, 121.4, 120.8, 27.8, 14.4. MS: *m/z* = 195 (M^+). Anal. calcd for $C_9H_9NS_2$ (195.02): Calcd. C 55.35, H 4.64, N 7.17. Found: C 55.48, H 4.59, N 7.11.

*3-Ethylbenzo[d]thiazole-2(3H)-thione (***3d***).* Colorless liquid, yield: 10%(ethyl acetate/petroleum ether = 1/30); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.42 (t, *J* = 8.0 Hz, 1H, H_{Ar}), 7.30 (q, *J* = 8.0 Hz, 1H, H_{Ar}), 7.25 (t, *J* = 8.0 Hz, 1H, H_{Ar}), 4.51 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 1.46 (t, *J* = 7.6 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8, 141.1, 128.0, 126.9, 124.6, 121.4, 112.2, 41.3, 11.8. MS: *m/z* = 195 (M^+). Anal. calcd for $C_9H_9NS_2$ (195.02): Calcd. C 55.35, H 4.64, N 7.17. Found: C 55.29, H 4.67, N 7.11.

*2-(Benzofuran-2-yl)-5-(ethylthio)-1,3,4-oxadiazole (***2e***).* Colorless solid, mp 62–64°C, yield: 73% (ethyl acetate/petroleum ether = 1/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 0.8 Hz, 1H, H_{furan}), 7.70–7.34 (m, 4H, H_{Ar}), 3.36 (q, *J* = 7.6 Hz,, 2H, CH_2CH_3), 1.58–1.52 (m, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 130.0, 124.7, 124.0, 122.2, 113.5, 112.0, 109.8, 108.8, 27.1, 14.6. MS: *m/z* = 246 (M^+). Anal. calcd for $C_{12}H_{10}NO_2S$ (246.05): Calcd. C 58.52, H 4.09, N 11.37. Found: C 58.64, H 4.04, N 11.43.

*5-(Benzofuran-2-yl)-3-ethyl-1,3,4-oxadiazole-2(3H)-thione (***3e***).* Colorless solid, mp 122–124°C, yield: 11% (ethyl acetate/petroleum ether = 1/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 0.8 Hz, 1H, H_{furan}), 7.72–7.29 (m, 4H, H_{Ar}), 4.26–4.20 (m, 2H, CH_2CH_3), 1.57–1.48 (m, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 155.8, 152.4, 140.1, 130.6, 127.7, 126.8, 124.3, 113.5, 112.0, 29.6, 12.5. MS: *m/z* = 246 (M^+). Anal. calcd for $C_{12}H_{10}NO_2S$ (246.05): Calcd. C 58.52, H 4.09, N 11.37. Found: C 58.62, H 4.13, N 11.45.

*O,O-Diethyl S-p-tolyl phosphorothioate (***2f***).* Yellow liquid, yield: 86% (ethyl acetate/petroleum ether = 1/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 0.8 Hz, *J* = 8.0 Hz, 2H, H_{Ar}), 7.15 (d, *J* = 8.0 Hz, 2H, H_{Ar}), 4.22–4.13 (m, 4H, OCH_2CH_3), 2.34 (s, 3H, CH_3), 1.35–1.23 (m, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 134.5, 130.1, 122.7, 63.9, 21.1, 16.0. MS: *m/z* = 260 (M^+). Anal. calcd for $C_{11}H_{17}PO_3S$ (260.05): Calcd. C 50.76, H 6.58, Found: C 50.88, H 6.53.

*4-(Ethylthio)-N-(1,2,2-trichlorovinyl)aniline (***2g***).* Yellow liquid, yield: 76% (ethyl acetate/petroleum ether = 1/15); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.32 (m, 2H, H_{Ar}), 6.58–6.55 (m, 2H, H_{Ar}), 3.96 (br, 1H, N*H*), 3.19–3.15 (m, 2H, CH_2CH_3), 1.30–1.25 (m, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 136.4, 133.6, 129.5, 120.8, 118.0, 115.6, 112.9, 38.1, 29.6, 14.6.0. MS: *m/z* = 281 (M^+) (60%), 283 (M + 2) (59%), 285 (M + 4) (24%), 266 (M – Me) (100%), 268 (M – Me + 2) (98%), 270 (M – Me + 4) (36%). Anal. calcd for $C_{10}H_{10}Cl_3NS$ (280.96): Calcd. C 42.50, H 3.75, N 3.96, Found: C 42.61, H 6.64, N 4.85.

Experimental Procedure for the Synthesis of Compound **2h**. To a solution of 4-aminobenzenethiol (**1g**) (1 mmol) and DMAP (0.2 mmol) in toluene (2 mL), diethyl phosphite (2 mmol) was added. After being stirred for 12 h at 110°C, the reaction mixture was concentrated under reduced pressure. Purification by chromatography on silica gel using ethyl acetate in petroleum ether (60–90°C) gave pure samples of product **2h**.

*4-(Ethylthio)benzenamine (***2h***).* Brown liquid, yield: 78% (ethyl acetate/petroleum ether = 1/20); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.28 (m, 2H, H_{Ar}), 6.52–6.48 (m, 2H, H_{Ar}), 3.68 (br, 2H, NH), 3.13 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 1.23 (d, *J* = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 134.4, 123.9, 115.4, 38.1, 14.6.0. MS: *m/z* = 153 (M^+). Anal. calcd for $C_8H_{11}NS$ (153.06): Calcd. C 62.70, H 7.24, N 9.14, Found: C 62.81, H 7.29, N 9.05.

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