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A simple, base-free preparation of *S*-aryl thioacetates as surrogates for aryl thiols

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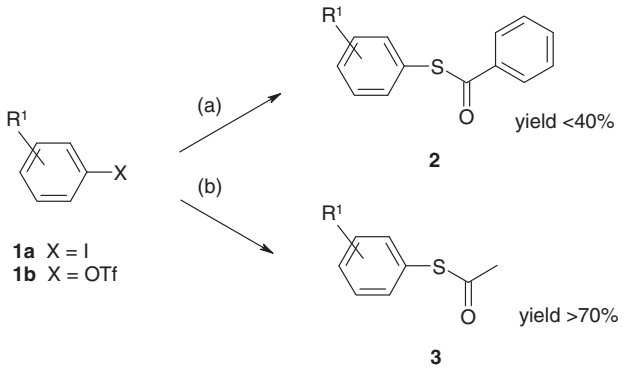
ABSTRACT

A mild method for the preparation of *S*-aryl thioacetates by hetero cross-coupling reactions of aryl bromides or aryl triflates with potassium thioacetate is described. The reaction proceeded smoothly in toluene at 110 °C, mediated by catalytic $Pd_2(dba)_3$ in combination with CyPF-*t*Bu as the ligand. Neither the presence of a base nor microwave conditions were required. The formed *S*-aryl thioacetate proved to be stable under flash chromatographic conditions and could be rapidly converted into the corresponding thiol under mildly basic conditions.

Thio esters and thiols constitute key chemotypes in the areas of organic and medicinal chemistry. These related motifs are frequently found in biologically active molecules[1] and polymeric material.[2] Moreover, such compounds are often used as starting materials for the synthesis of heterocyclic ring systems.[3] However, their preparation—in contrast to the corresponding oxygen- and nitrogen-containing compounds—is generally less straightforward. Nucleophilic substitution reactions,[4] lithiation chemistry[5] and, more recently, palladium-[6] or copper-catalyzed[7] hetero cross-coupling strategies constitute frequently applied methods for the introduction of thio moieties.

Recently, a number of arylbenzyl thioethers was required for one of our research projects. Based on our interest in palladium- and copper-catalyzed chemistry,[8] it was reasoned that there are two ways to realize their synthesis, viz. a hetero cross-coupling reaction of an aryl halide or aryl triflate with a benzyl thiol, or a more classical benzylation reaction between an aryl thiol or a protected aryl thiol and a benzyl halide. In the latter option, the (protected) aryl thiol needs to be prepared from the corresponding halide or triflate. Since functionalized benzyl halides, in general, have a broader commercial availability in comparison with the corresponding benzyl thiols, it was decided to pursue the latter option. An additional advantage would be the avoidance of malodorous benzyl thiols.

Several Letters have described the palladium- or copper-mediated conversion of aryl halides into the corresponding protected thiol.[3d,3g,6d,7e,9] Since it is known[6b] that the poisoning effect of sulfur can be troublesome in palladium-catalyzed-cross-coupling reactions, the copper-catalyzed method described by Sawada[7e] (thiobenzoic acid as a thiol surrogate) was initially investigated (Scheme 1). Although the application of this method on our aryl iodide derivative resulted in incomplete conversion of **1a** and a low chemical yield (<40%) of **2**, we managed to improve the course of an analogous *S*-aryl ester formation and its yield (>70%) by substitution of thiobenzoic acid by the more easy to handle potassium thioacetate as the thiol surrogate to furnish **3** (Scheme 1). In spite of these initially encouraging results, several disadvantages remained to be improved. The copper-catalyzed method proved only



Scheme 1. For **1a**: (a) reagents and conditions: Sawada[7e]: CuI/1,10-phenanthroline, thiobenzoic acid, *i*-Pr_2NEt, toluene, 110 °C, 24 h. For **1a**: (b) reagents and conditions: CuI/1,10-phenanthroline, potassium thioacetate, *i*-Pr_2NEt, toluene, 110 °C, 24 h; for **1b**: see the conditions described in the text.

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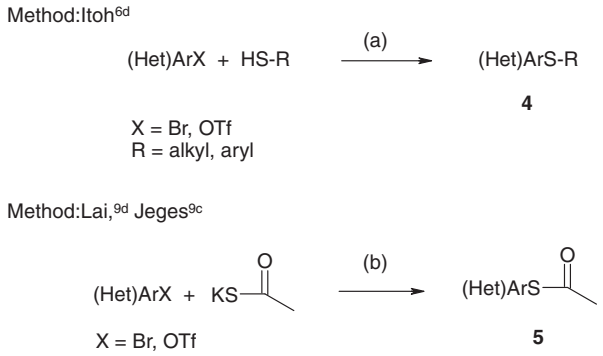


Scheme 2. (a) $Pd_2(dba)_3$/Xantphos, *i*-Pr_2NEt, 1,4-dioxane, reflux; (b) $Pd_2(dba)_3$/Xantphos, *i*-Pr_2NEt, 1,4-dioxane, microwave, 160 °C.

to be successful with aryl iodides as starting materials. Therefore, further attention was focused on a palladium-catalyzed conversion of aryl triflates—which can be easily prepared from the corresponding phenols[10]—and readily available aryl bromides. Our starting point was the procedure of Itoh[6d] who described the conversion of aryl bromides or aryl triflates into the corresponding thioethers **4** by reacting them with a suitable aryl or alkyl thiol using $Pd_2(dba)_3$/Xantphos, *i*-Pr_2NEt, and 1,4-dioxane as optimal conditions (Scheme 2). More recently, a variation of Itoh's method was applied by Lai[9c] and Jeges,[9b] applying potassium thioacetate as the thiol source to deliver compounds of general formula **5**. However, this reaction was reported to be successful only under microwave heating conditions at 160 °C (Scheme 2). As many synthetic chemists still prefer oil bath heating above microwave heating, and given the fact that many laboratories are not equipped with dedicated microwave instruments, triflate **1b** was reacted with potassium thioacetate using oil bath heating and the conditions of Lai.[9c] Unfortunately, an incomplete conversion into **3** was found. Moreover, the reproducibility of this particular reaction proved to be troublesome, thereby precluding its general use.

Therefore, it was decided to shift our attention to the pioneering work of Hartwig in the area of palladium-catalyzed thioetherification of aryl halides and aryl triflates.[6a,9a,11] Key to his success was the use of the commercially available (*R*)-1-[(S_p)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine as the ligand[12] (further abbreviated as CyPF-*t*Bu, Fig. 1) in combination with a suitable Pd precursor, base, and solvent. Very recently, Hartwig also reported this method for the preparation of a number of phenyl triisopropylsilyl sulfides (ArS-TIPS) as thiol surrogates.[9a] However, in some cases their ArS-TIPS derivatives suffered from a lack of stability during purification. Moreover, the high costs of the required TIPS-SH reagent in comparison with potassium thioacetate prompted us to further explore the hetero cross-coupling reaction between the triflate **1b** and potassium thioacetate, mediated by $Pd_2(dba)_3$/CyPF-*t*Bu. A brief survey of reaction conditions revealed a clean conversion in toluene at a temperature of 110 °C within 16 h. In contrast to other literature methods, no additional base was required. It is also interesting to note that **3** remained stable during flash chromatographic purification. These encouraging

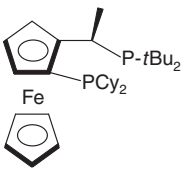


Figure 1.

results prompted us to further investigate the scope and generality of this mild synthetic method by reacting a number of (mostly) commercially available aryl bromides **6**–**14**, **16**, and **19**, aryl triflates **15**, **17**, and **20**–**23**, and the aryl chloride **18** with potassium thioacetate. As a general procedure, all the experiments were carried out with 1 mmol of aryl bromide, aryl triflate or aryl chloride, 2 mmol of potassium thioacetate, 2.5 mol % of $Pd_2(dba)_3$, and 5 mol % of CyPF-*t*Bu in 15 ml of toluene at 110 °C for 24 h.[13] The results are disclosed in Table 1.[14]

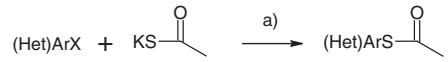
Moderate to good yields were obtained using aryl- or heteroaryl bromides **6**–**12**, and **16**. Common functional groups for example NH_2 or the base-sensitive *N*-acetyl moiety proved to be well-tolerated (entries 3 and 4). No side reactions were detected. Interestingly, we observed that both the formamides **11** and **29** existed in two conformations, based on their ^1H NMR spectra. Additionally, during the conversion of **29**, the *N*-formyl group was partially transformed into the corresponding *N*-acetyl moiety (see compound **27**). As both **9** and **11** did not dissolve readily in toluene at room temperature, these compounds were dissolved at 100 °C, followed by the simultaneous addition of potassium thioacetate, $Pd_2(dba)_3$, and CyPF-*t*Bu at the same temperature. Of particular interest is the conversion of **10** into **28**. The sensitive *N*-Cbz group survived our neutral reaction conditions, which is in contrast with the reported result of Lai.[9c] In accordance with Lai's findings, nitro-containing substrates were unsuitable as starting materials, besides the starting compound, only a low yield of product was obtained (entries 8 and 9). The presence of an ethyl ester moiety was also tolerated; no trace of any saponification product was detected (entry 11). Unexpectedly, the conversion of **19** into **34** was disappointing (entry 14). Aryl triflates generally reacted smoothly under the neutral conditions (entries 12 and 15, 16–18). Although the conversion of **20** was troublesome, prior protection of **20** as its *N*-Boc carbamate **21** raised the yield of the *S*-indolyl thioacetate formation from 16% to 79% (entries 15 and 16). In accordance with expectation, it was not possible to convert **15** into **32** (entry 10), only starting material was recovered. The aryl chloride **18** was also converted, in a modest yield of 36% into **33**, despite the fact that $Pd_2(dba)_3$/CyPF-*t*Bu is generally considered to be a suitable system for the conversion of aryl chlorides (entry 13). Substitution of toluene for the higher boiling xylene and raising the temperature to 125 °C did not turn out to be beneficial for the conversion of **18**.

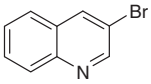
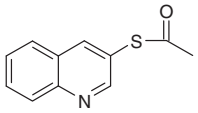
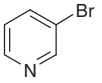
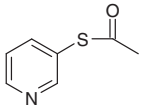
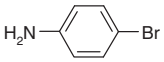
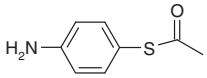
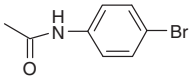
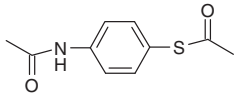
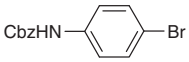
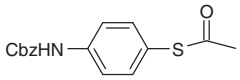
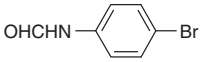
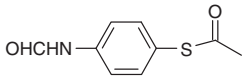
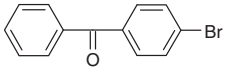
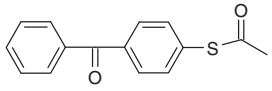
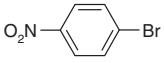
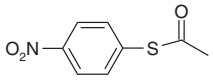
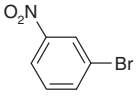
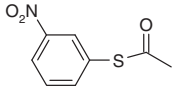
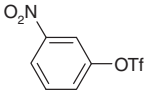
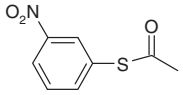
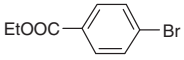
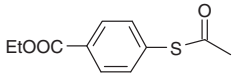
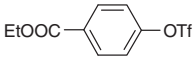
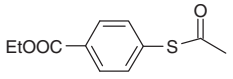
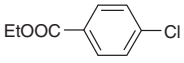
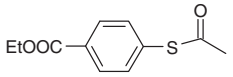
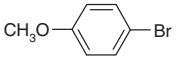
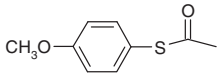
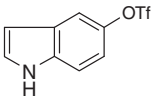
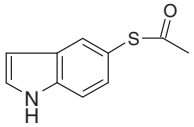
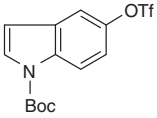
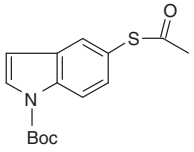
The palladium precursor effect found during this investigation was of interest. Substitution of $Pd_2(dba)_3$ for $Pd(OAc)_2$ was not beneficial. A dramatic effect was seen for the conversion of **7** into **25**. The yield dropped from 80% to a negligibly low value. The analogous reaction of **13** resulted in the recovery of starting material. These results indicated that the in situ reduction of Pd(II) into Pd(0) did not occur under our reaction conditions. Using 10 mol % of phenylboronic acid as a possible reductor for $Pd(OAc)_2$[15] for the conversion of **17** into **33** was not successful, and no reaction was observed.

Finally, we briefly investigated the conversion of **6** into **24** using microwave conditions (50 min, 160 °C in 1,4-dioxane). Surprisingly, no improvement was found. Besides **24** (37 mol % based on LC–MS), bromide **6** was still present (50 mol % based on LC–MS) together with the dimeric 3-(quinolin-3-ylsulfanyl)quinoline (13 mol % based on LC–MS).

The development of our general and mild procedure to convert aryl bromides and aryl triflates into their corresponding *S*-aryl thioacetates **24**–**38** prompted their further transformations into the corresponding thiols under mild basic conditions. Deprotection of **24**, followed by in situ benzylation of the so formed 3-quinolinylmercaptan, at 0 °C with benzyl bromide in ethanol (containing 1.1 mol equivalents of NaOH), resulted in clean and rapid conversion into sulfide **39** in an overall yield of 72% (Scheme 3).[16] In this respect, the *S*-aryl thioacetate moiety is preferable over *S*-TIPS as a

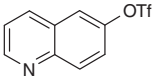
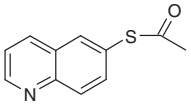
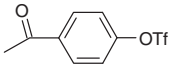
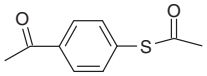
Table 1
Reagents and conditions: (a) 1 mol equivalent of (Het)ArX, 2 mol equivalent of KSAc, 2.5 mol % $Pd_2(dba)_3$, 5 mol % CyPF-*t*Bu, 15 ml of toluene, 110 °C, 24 h



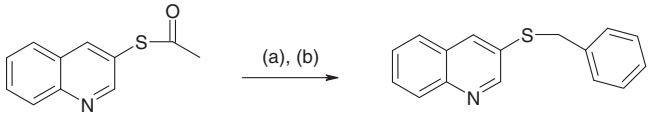
Entry	(Het)ArX		Product		Yield[a] (%)
1		**6**		**24**	90[b]
2		**7**		**25**	80
3		**8**		**26**	60
4		**9**		**27**	72
5		**10**		**28**	55
6		**11**		**29**	90[c,d]
7		**12**		**30**	70
8		**13**		**31**	15
9		**14**		**32**	13
10		**15**		**32**	0
11		**16**		**33**	67[e]
12		**17**		**33**	58[f]
13		**18**		**33**	36[f]
14		**19**		**34**	20
15		**20**		**35**	16
16		**21**		**36**	79

(*continued on next page*)

Table 1 (*continued*)

Entry	(Het)ArX		Product		Yield[a] (%)
17		**22**		**37**	69
18		**23**		**38**	67

[a] Isolated yield of pure compounds.
[b] Running the reaction in 1,4-dioxane resulted in incomplete conversion.
[c] Product exists in two conformations in the ratio 3:2.
[d] Contaminated with 15 mol % of **27**.
[e] Contaminated with 4 mol % of dibenzylideneacetone.
[f] Contaminated with 30 mol % of dibenzylideneacetone.



24 **39**

Scheme 3. Reagents and conditions: (a) 1 mol equivalent of **24**, 1.1 mol equivalent of NaOH, EtOH, 0 °C, 10 min; (b) 1.1 mol equivalent of BnBr, 0 °C, 10 min, 72%.

thiol surrogate since the *S*-TIPS moiety was reported to require four equivalents of CsF for deprotection.[9a] Finally, this procedure was successfully applied within our research projects resulting in a large number of arylbenzyl thioethers (unfortunately, for patent reasons, we are not able to report these data).

In conclusion, a novel and mild palladium-catalyzed method is described for the smooth conversion, under neutral conditions, of a variety of aryl bromides and aryl triflates into the corresponding *S*-aryl thioacetates, which can be regarded as thiol surrogates. All the prepared *S*-aryl thioacetates were purified by flash chromatography over silica gel without concomitant deprotection to the thiol. In contrast with the existing method, microwave heating was not needed. Moreover, during our investigation, it was found that the yield in some cases could be increased by adding more $Pd_2(dba)_3$/CyPF-*t*Bu (data not shown). Therefore, our procedure constitutes a straightforward, mild, and cheap alternative to Hartwig's[9a] *S*-TIPS methodology. It can be anticipated that besides a benzylation after the deprotection step, alkylations, acylations, ketone synthesis[17] or new cross-coupling reactions with a variety of aryl bromides or aryl triflates should be feasible. Such chemistry will be investigated in more detail in the near future.

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References and notes

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12. Commercially available, for example, at Aldrich, catalog number 88733 or STREM Chemicals, catalogue number 26-0975.
13. *General procedure for the hetero cross-coupling with potassium thioacetate* (Table 1, entry 1): A dried 50 ml, three-necked reaction vessel was charged with degassed toluene (15 ml) followed by the addition of **6** (208 mg, 1 mmol) resulting in a clear solution. After addition of $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and CyPF-*t*Bu (27.7 mg, 0.05 mmol), the mixture was stirred under a nitrogen atmosphere for 5 min at room temperature. KSAc (228 mg, 2 mmol) was added and the mixture was heated in a pre-heated oil bath at 110 °C for 24 h. After cooling to room temperature, Et_2O was added. Undissolved salts were removed by filtration and the remaining organic layer was concentrated in vacuo. The obtained crude **24** was further purified by flash chromatography [silica gel 60 (0.040–0.063 nm, Merck)] eluting with CH_2Cl_2–acetone, 95:5 (v/v), to give 183 mg of pure **24** (90%).
14. The compounds described in Table 1, which are known in the literature (**25**–**27**, **31**, **32**, **34**, **38**) exhibited spectral properties consistent with the assigned structures. Spectral data are given for the compounds described in Table 1, which to the best of our knowledge are unknown in the literature. *Compound* **24**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (s, 3H), 7.60 (br t, J = 8 Hz,1H), 7.76–7.81 (m, 1H), 7.83 (d, J = 8 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.26 (d, J = 2 Hz, 1H), 8.82 (d, J = 2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.36, 120.94, 126.24, 126.83, 126.99, 128.39, 129.64, 141.10, 146.65, 152.72, 191.86. HRMS (ES+): calcd for $C_{11}H_{11}NOS$ $(M+H)^+$: 204.0483; found: 204.0479. *Compound* **28**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 5.21 (s, 2H), 6.74 (br s, 1H), 7.32–7.41 (m, 7H), 7.45 (br d, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.00, 66.16, 117.97, 120.60, 127.32, 127.42, 127.63, 134.42, 134.79, 138.18, 152.00, 193.98. HRMS (ES+): calcd for $C_{16}H_{16}NO_3S$ $(M+H)^+$: 302.0851; found: 302.0832. *Compound* **29**, exists as two conformations according to NMR data: (a) 60 mol %, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 7.36 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 2H), 8.05 (br s, 1H), 8.35 (d, J = 2 Hz, 1H). (b) 40 mol %, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.11 (d, J = 8 Hz, 2H), 7.39 (d, J = 8 Hz, 2H), 8.09 (br s, 1H), 8.82 (d, J = 2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.16, 118.84, 120.46, 123.01, 123.90, 135.41, 136.09, 138.08, 138.31, 159.24, 162.18, 194.57, 195.26. HRMS (ES+): calcd for $C_9H_{10}NO_2S$ $(M+H)^+$: 196.0432; found: 196.0419. *Compound* **30**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3H), 7.47–7.56 (m, 4H), 7.58–7.64 (m, 1H), 7.79–7.85 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.46, 128.97, 130.00, 130.51, 132.70, 132.98, 133.89, 137.15, 138.03, 192.76, 195.86. HRMS (ES+): calcd for $C_{15}H_{13}O_2S$ $(M+H)^+$: 257.0636; found: 257.0619. *Compound* **33**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J = 8 Hz, 3H), 2.45 (s, 3H), 4.36–4.42 (m, 2H), 7.49 (d, J = 8 Hz, 2H), 8.07 (d, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.28, 29.40, 60.21, 129.36, 130.15, 132.37, 132.96, 164.88, 191.71. HRMS (ES+): calcd for $C_{11}H_{13}O_3S$ $(M+H)^+$: 225.0585; found: 225.057. *Compound* **35**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 6.54 (m, 1H), 7.15–7.19 (m, 2H), 7.33 (d, J = 8 Hz, 1H), 7.01 (br s, 1H), 8.35 (br s, 1H). HRMS (ES+): calcd for $C_{10}H_{10}NOS$ $(M+H)^+$: 192.0483; found: 192.0502. ^{13}C NMR data not available. *Compound* **36**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 9H), 2.42 (s, 3H), 6.57 (d, J = 4 Hz, 1H), 7.33 (dd, J = 8 and 2 Hz, 1H), 7.61–7.65 (m, 2H), 8.18 (br d, J = 8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.27, 30.06, 84.17, 107.08, 115.96, 121.31, 126.89, 127.57, 130.29, 131.42, 135.62, 149.47, 195.22. HRMS (ES+): calcd for $C_{15}H_{18}NO_3S$ $(M+H)^+$: 292.1007; found: 292.1010. *Compound* **37**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 (s, 3H), 7.44 (dd, J = 8 and 4 Hz, 1H), 7.69 (dd, J = 8 and 2 Hz, 1H), 7.94 (br s, 1H), 8.15 (t, J = 8 Hz, 2H), 8.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.33, 120.66, 125.39, 127.39, 129.37, 133.10, 133.51, 134.99, 147.08, 150.51, 192.57. HRMS (ES+): calcd for $C_{11}H_{10}NOS$ $(M+H)^+$: 204.0483; found: 204.0466. *Compound* **21** (starting material for **36**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 9H), 6.60 (d, J = 4 Hz, 1H), 7.21 (dd, J = 8 and 2 Hz, 1H), 7.48 (d, J = 2 Hz, 1H), 7.70 (d, J = 4 Hz, 1H), 8.21 (br d, J = 8 Hz, 1H). ^{13}C data and HRMS data not available.
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16. *Typical procedure for the preparation of compound* **39**: A dried 50 ml reaction vessel was charged with thioacetate **24** (115 mg, 0.55 mmol). Under ice-bath cooling, a solution of NaOH (25 mg, 0.62 mmol) in anhydrous EtOH (5 ml) was added. The obtained solution was stirred under a nitrogen atmosphere at 0 °C until deprotection of the *S*-acetyl moiety was complete (10 min, monitored by LC–MS). Benzyl bromide (106 mg, 0.62 mmol) was added, and after additional stirring at 0 °C for 10 min, repeated LC–MS indicated total conversion into **39**. The reaction mixture was diluted with EtOAc, followed by washing with brine (2×10 ml). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography [silica gel 60 (0.040–0.063 nm, Merck)] eluting with CH_2Cl_2–acetone, 95:5 (v/v) gave 100 mg of pure **39** (72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 (s, 2H), 7.21–7.31 (m, 5H), 7.53 (t, J = 8 Hz, 1H), 7.65–7.70 (m, 2H), 7.98 (d, J = 2 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 8.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.35, 127.11, 127.13, 127.50, 128.06, 128.65, 128.88, 129.27, 129.33, 129.86, 136.66, 136.77, 146.52, 152.15. HRMS (ES+): calcd for $C_{16}H_{14}NS$ $(M+H)^+$ 252.0487; found: 252.0825.
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