Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3033–3037

Efficient preparation of *S*-aryl thioacetates from aryl halides and potassium thioacetate

Chunqiu Lai* and Bradley J. Backes

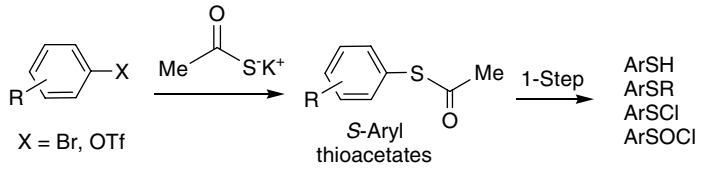
Metabolic Disease Research, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098, USA

Received 3 October 2006; revised 24 February 2007; accepted 26 February 2007
Available online 2 March 2007

Abstract—A method for the preparation of *S*-aryl thioacetates using palladium-mediated couplings of aryl bromides and aryl triflates with potassium thioacetate as an inexpensive thiol source was developed. Electron withdrawing groups, electron donating groups and heterocyclic substrates were tolerated in the reaction conditions, affording the corresponding products in good to excellent yields. This method was applied to the preparation of novel sulfone-containing DPP-IV inhibitors.

Compounds that possess arylsulfur-containing functional groups have found use in multiple applications, including those in biological, pharmaceutical and materials areas.[1] Accordingly, methods to construct the aryl–sulfur bond are of high utility. In spite of this, relatively few efficient and general methods to prepare versatile arylthiol equivalents from readily available starting materials have been developed. Classical preparations generally feature the trapping of metalated aryl groups with elemental sulfur to afford arylthiols.[2] However, these transformations cannot be applied for those aryl substrates bearing sensitive functionalities such as aldehyde, ketone and ester groups. More modern procedures utilize specialized sulfur reagents that can be coupled with aryl halides to afford stable intermediates. A second step is used to reveal the arylthiol functionality.[3] For example, *iso*-octyl-3-mercaptopropionate[3e] and 2-(4-pyridyl)ethanethiol[3f] can be coupled to aryl bromides to furnish intermediates that are susceptible to β-elimination. Treatment with sodium *tert*-butoxide then gives the corresponding arylthiol products.[3h] While effective, these specialized sulfur reagents are not simple and low cost thiol sources. We reasoned that the coupling of inexpensive thioacetic acid with aryl halides would be a powerful alternative to form the aryl–sulfur bond (Scheme 1).[4] The resulting *S*-aryl thioacetates are versatile intermediates from which a number of sulfur-containing functional groups including arylthiols (ArSH),[5] aryl sulfenyl chlorides (ArSCl),[6] aryl sulfinyl chlorides (ArSOCl)[7] and aryl alkyl sulfides (ArSR)[8] can be accessed in a straightforward manner. Here, we report a general Pd-catalyzed coupling of aryl bromides/triflates with inexpensive potassium thioacetate to give *S*-aryl thioacetates under microwave conditions (Scheme 1).

We used the catalyst system ($Pd_2(dba)_3$–Xantphos) reported by Ioth and Mase[3h] as a starting point to investigate the coupling efficiency of bromobenzene with potassium thioacetate (Table 1). Under refluxing conditions with 1,4-dioxane as solvent (100 °C), we were

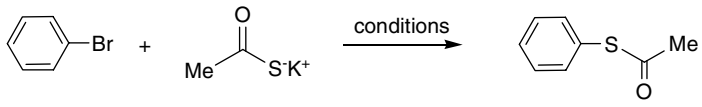


Scheme 1. Preparation of versatile *S*-aryl thioacetates.

* Corresponding author. Tel.: +1 847 935 6567; fax: +1 847 938 1674; e-mail: chunqiu.lai@abbott.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.02.128

Table 1. Evaluation of reaction conditions for the formation of *S*-phenyl thioacetate

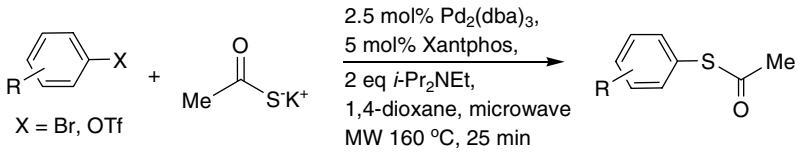


Entry	Conditions[a]	Yield[b] (%)
1	$Pd_2(dba)_3$, Xantphos, *i*-Pr_2NEt, 1,4-dioxane, 100 °C, 1d	30
2	$Pd_2(dba)_3$, Xantphos, *i*-Pr_2NEt, diglyme, 150 °C, 1d	nd
3	$Pd_2(dba)_3$, Xantphos, *i*-Pr_2NEt, DMF, 150 °C, 1d	nd
4	$Pd_2(dba)_3$, Xantphos, *i*-Pr_2NEt, NMP, 150 °C, 1d	nd
5	$Pd_2(dba)_3$, Xantphos, *i*-Pr_2NEt, 1,4-dioxane, microwave, 160 °C, 25 min	89
6	1,4-Dioxane, microwave, 160 °C, 25 min	nd
7	$Pd_2(dba)_3$, *i*-Pr_2NEt, 1,4-dioxane, microwave, 160 °C, 25 min	nd
8	$Pd_2(dba)_3$, Xantphos, 1,4-dioxane, microwave, 160 °C, 25 min	5

[a] Reactions were performed using 2.5 mol % catalyst, 5 mol % ligand, 1.5 equiv of potassium thioacetate, 2.0 equiv of Hunig's base and 3.6 mL of solvent with 1.0 mmol of bromobenzene.
[b] Isolated yield.

pleased to observe partial conversion to give *S*-phenyl thioacetate (30%) (entry 1). This result was encouraging and we reasoned that the conversion could be increased through better dissolution of potassium thioacetate. To this end, various aprotic solvents and reaction temperatures were screened. Diglyme at 150 °C gave no detectable amount of the desired product (entry 2). Similarly poor results were observed for DMF and NMP (entries 3, 4). However, the subjection of the reaction mixture to microwave heating at 160 °C with 1,4-dioxane as solvent afforded the desired product in an excellent yield (entry 5, 89%).

Table 2. Pd-catalyzed coupling of aryl bromides/triflates potassium thioacetate under microwave conditions



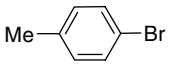
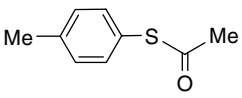
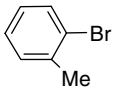
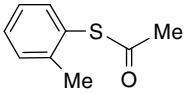
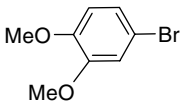
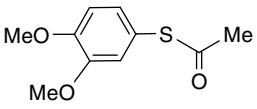
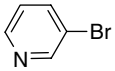
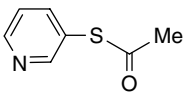
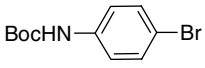
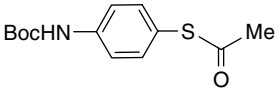
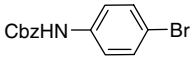
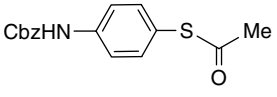
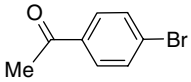
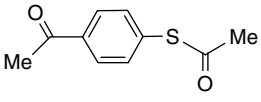
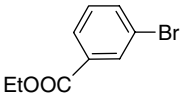
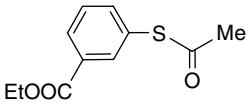
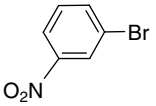
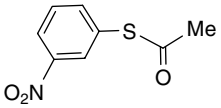
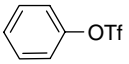
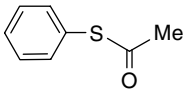
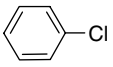
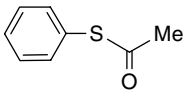
Entry	ArX	Product	Yield[a] (%)
1			75
2			72
3			51
4			85
5			71
6			—
7			65

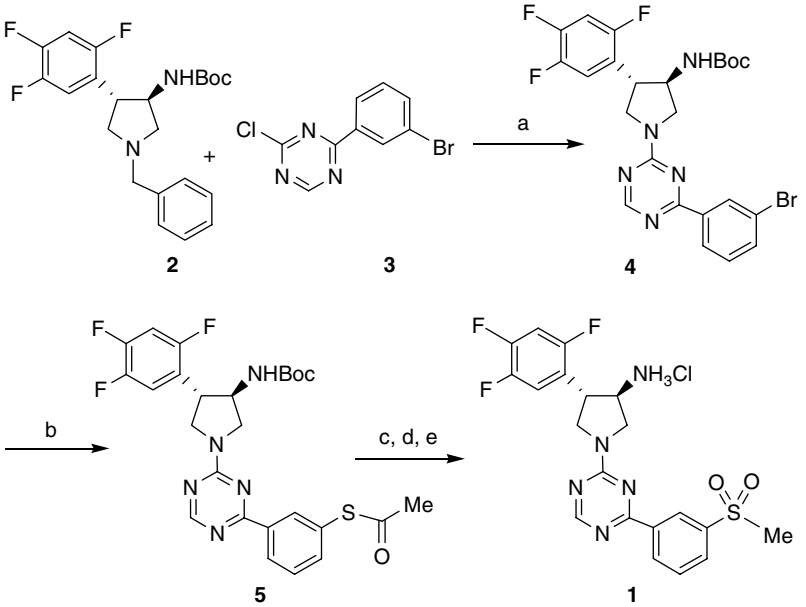
Table 2 (*continued*)

Entry	ArX	Product	Yield[a] (%)
8			88
9			—
10			91
11			—

[a] Isolated yield.

In order to investigate the requirements of the transformation, we performed reactions in the absence of $Pd_2(dba)_3$–Xantphos and Hunig's base (entry 6), ligand Xantphos (entry 7), or Hunig's base (entry 8). None of these reaction conditions were effective. Finally, it should be noted that the use of thioacetic acid, rather than potassium thioacetate, employing our best conditions ($Pd_2(dba)_3$, Xantphos, *i*-Pr_2NEt, 1,4-dioxane, microwave, 160 °C, 25 min) did not yield any product.

With the optimized reaction conditions in hand, we then explored the scope of the transformation by coupling various functionalized aryl bromides and aryl triflates with potassium thioacetate (Table 2).[9] Sterically hindered *ortho*-bromotoluene provided the corresponding product in good yield (entry 2). Electron rich 3,4-dimethoxybromobenzene coupled with moderate efficiency (entry 3, 51%), while the electron poor heterocycle 3-bromopyridine gave a good yield of thioacetate product (entry 4, 85%). Common functional groups such as *N*-Boc carbamates, ketones and ethyl esters proved to be well-tolerated under our reaction conditions, as exemplified by entries 5, 7 and 8. However, both *N*-Cbz carbamate (entry 6) and nitro-containing substrates (entry 9) provided no reaction products due to either cross-reaction of these functionalities with potassium thioacetate or decomposition. In addition, the protocol can be applied with aryl triflates (entry



Scheme 2. Reagents and conditions (a) CH_3CN, 80 °C, 0.5 h, 83%; (b) CH_3COSK, $Pd_2(dba)_3$, Xantphos, *i*-Pr_2NEt, 1,4-dioxane, microwave, 160 °C, 25 min, 87%; (c) CH_3I, NaOH (1 N), EtOH, 0 °C, 1 h; (d) *m*-CPBA, CH_2Cl_2, rt, 50 min; (e) HCl/1,4-dioxane (4 N), rt, 2 h, (84%—three steps).

10, 91%). Aryl chlorides did not couple under these conditions, thus defining the limits of reactivity (entry 11).

These methods were applied to the development of pyrrolidine-constrained phenethylamine DPP-IV inhibitors such as **1**.[10] A flexible and efficient synthesis of compound **1** is shown in Scheme 2.[11] Briefly, pyrrolidine **2**[10] was treated with bromo-substituted triazine chloride **3**[12] to provide **4** in high yield (83%). This efficient transformation proceeded with quaternization of the amine followed by debenzylation.[13] Compound **4** was then coupled with potassium thioacetate under our optimized reaction conditions to form key intermediate **5** in 87% yield. Compound **5** was cleanly converted to the corresponding methyl sulfide via one-pot deacylation/alkylation with MeI.[8] Finally, oxidation of the methyl sulfide with *m*-chloroperoxybenzoic acid followed by a deprotection step provided the desired product **1** in high yield (84% from **5**).

In summary, we have developed an efficient and functional group compatible method for the formation of aryl–sulfur bonds through the coupling of aryl bromides and aryl triflates with an inexpensive thiol source. The *S*-aryl thioacetate products that this method provides are versatile intermediates for the preparation of a range of sulfur-containing functional groups. We have applied these methods to the synthesis of DPP-IV inhibitors that contain sensitive functionality. Further improvement and applications of this protocol will be reported in due course.

Acknowledgements

The authors thank the staff of Abbott Structural Chemistry Department for obtaining the spectral data, and Dr. Andrew J. Souers and Dr. Thomas W. von Geldern for their valuable comments.

References and notes

1. (a) Lindstd, R. I.; McKinley-Mckee, J. S. *Eur. J. Biochem.* **1996**, *241*, 142–148; (b) Karyakin, A. A.; Presnova, G. V.; Rubtsova, M. Y.; Egorov, A. M. *Anal. Chem.* **2000**, *72*, 3805–3811; (c) Winn, M.; Reily, E. B.; Liu, G.; Huth, J. R.; Jae, H.-S.; Freemam, J.; Pei, Z.; Xin, Z.; Lynch, J.; Kester, J.; von Geldern, T. W.; Leitza, S.; DeVries, P.; Dickinson, R.; Mussatto, D.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 4393–4403; (d) Liu, G.; Link, J. T.; Pei, Z.; Reilly, E. B.; Leitza, S.; Nguyen, B.; Marsh, K. C.; Okasinski, G. F.; von Geldern, T. W.; Ormes, M.; Fowler, K.; Gallatin, M. *J. Med. Chem.* **2000**, *43*, 4025–4040; (e) Li, Z.; Yang, Q.; Qian, X. *Bioorg. Med. Chem. Lett.* **2005**, *13*, 4864–4870; (f) Beard, R. L.; Colon, D. F.; Song, T. K.; Davies, P. J. A.; Kochhar, D. M.; Chandratna, R. A. S. *J. Med. Chem.* **1996**, *39*, 3556–3563; (g) Wang, Y.; Chackalmannil, S.; Chang, W.; Greenlee, W.; Ruperto, V.; Duffy, R. A.; McQuade, R.; Lachowicz, J. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 891–894; (h) Pinchart, A.; Dallaire, C.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 543–546; (i) Yu, C. J.; Chong, Y.; Kayyem, J. F.; Gozin, M. *J. Org. Chem.* **1999**, *64*, 2070–2079.
2. Patai, S. *The Chemistry of the Thiol Group*; John Wiley & Sons: London, 1974; Chapter 4, Part 1, pp 163–269.
3. (a) Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* **1980**, *21*, 3099–3100; (b) Pinchart, A.; Dallaire, C.; Bierbeek, A. V.; Gingras, M. *Tetrahedron Lett.* **1999**, *40*, 5479–5482; (c) Takagi, K. *Chem. Lett.* **1985**, 1307–1308; (d) Flatt, A. K.; Tour, J. M. *Tetrahedron Lett.* **2003**, *44*, 6699–6702; (e) Becht, J.-M.; Wangner, A.; Mioskowski, C. *J. Org. Chem.* **2003**, *68*, 5758–5761; (f) Katritzky, A. R.; Khan, G. R.; Schwarz, O. A. *Tetrahedron Lett.* **1984**, *25*, 1223–1226; (g) Rane, A. M.; Miranda, E. I.; Soderquist, J. A. *Tetrahedron Lett.* **1994**, *35*, 3225–3226; (h) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587–4590.
4. *S*-Aryl thioacetates were prepared in 40–60% yield by the treatment of arenediazonium tetrafluoroborates with commercial potassium thioacetate. Petrillo, G.; Novi, M.; Garbarino, G.; Filiberti, M. *Tetrahedron Lett.* **1988**, *29*, 4185–4188.
5. (a) MacCoss, R. N.; Henry, D. J.; Brain, C. T.; Ley, S. V. *Synlett* **2004**, 675–678; (b) Jin, C. K.; Jeong, H. J.; Kim, M. K.; Kim, J. Y.; Yoon, Y.-J.; Lee, S.-G. *Synlett* **2001**, 1956–1958.
6. Thea, S.; Cevasco, G. *Tetrahedron Lett.* **1988**, *29*, 2865–2866.
7. Thea, S.; Cevasco, G. *Tetrahedron Lett.* **1987**, *28*, 5193–5194.
8. Sawicki, E. *J. Org. Chem.* **1956**, *21*, 271–273.
9. All microwave reactions were performed using a Personal Chemistry Emrys™ Optimizer in a septa capped 2–5 mL Biotage™ microwave tube with magnetic stirring. Power required to maintain target temperature was controlled by Emrys™ Optimizer Software. The synthesis of representative compound thioacetic acid *S*-(4-*tert*-butoxycarbonylamino-phenyl) ester (Table 2, entry 5): (4-Bromophenyl)carbamic acid *tert*-butyl ester (270 mg, 1.0 mmol), potassium thioacetate (170 mg, 1.5 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and Xantphos (29 mg, 0.050 mmol) were placed in a 2–5 mL Biotage™ microwave tube capped with a rubber septum. The tube was evacuated under vacuum and refilled with nitrogen three times. *i*-Pr_2NEt (350 μL, 2.0 mmol) and degassed dry 1,4-dioxane (3.6 mL) were added to the tube and the rubber septum was quickly replaced with a microwave tube cap. The reaction mixture was heated in a microwave at 160 °C for 25 min. The reaction mixture was partitioned between EtOAc and water. The aqueous phase was extracted again with EtOAc. The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (0–20% EtOAc/hexanes) to give thioacetic acid *S*-(4-*tert*-butoxycarbonylaminophenyl) ester (190 mg, 71%). ^1H NMR (300 MHz, CD_3OD) δ 7.43–7.51 (m, 2H), 7.24–7.31 (m, 2H), 2.35 (s, 1H), 1.51 (s, 9H) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ 196.75, 154.88, 142.14, 136.31, 122.01, 119.98, 81.15, 29.85, 28.66 ppm. MS (+ESI) *m*/*z* 285.0 ($M + NH_4^+$). Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.4; H, 6.41; N, 5.24. Found: C, 58.35; H, 6.20; N, 5.18.
10. Backes, B. J.; Longenecker, K.; Hamilton, G. L.; Stewart, K.; Lai, C.; Kopecka, H.; von Geldern, T. W.; Madar, D. J.; Pei, Z.; Lubben, T. H.; Zinker, B. A.; Tian, Z.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Kempf-Grote, A. J.; Black-Schaefer, C.; Sham, H. L.; Trevillyan, J. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2005–2012.
11. *Preparation of* **1**: A mixture of **2** (1.30 g, 4.80 mmol) and **3** (2.0 g, 4.80 mmol) in CH_3CN (16 mL) was stirred at 80 °C for 30 min.[13] After cooling to room temperature, the solids were collected and washed with hexanes three times. Compound **4** was obtained as a white solid (2.20 g, 83% yield). Using our coupling procedure (Ref. 9), **4** (110 mg,

0.20 mmol) was coupled with potassium thioacetate to afford intermediate **5** (95 mg, 87%). A mixture of **5** (27 mg, 0.050 mmol), CH_3I (8.5 mg, 0.060 mmol) and NaOH (1 N, 60 μL, 0.060 mmol) in EtOH (0.3 mL) was stirred at 0 °C for 1 h. The reaction mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4 and concentrated in vacuo to provide the corresponding methyl sulfide (27 mg, 100%). To a solution of the methyl sulfide (27 mg, 0.050 mmol) in CH_2Cl_2 (0.6 mL) was added *m*-CPBA (70–75%, 26 mg, 0.10 mmol). After stirring at 50 °C for 50 min, the reaction mixture was quenched with $NaHCO_3$ (1 N) and extracted with ethyl acetate. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography on silica gel (30–80% EtOAc/hexanes) to give the methyl sulfoxide (23 mg, 84%). A solution of the methyl sulfoxide (23 mg, 0.042 mmol) in HCl/1,4-dioxane (4 N, 0.1 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under vacuum to afford **1** (21 mg, 100%). ^1H NMR (300 MHz, CD_3OD) δ 8.86–8.95 (m, 1H), 8.78–8.85 (m, 1H), 8.63–8.74 (m, 1H), 8.17–8.27 (m, 1H), 7.78–7.89 (m, 1H), 7.55–7.65 (m, 1H), 7.26–7.37 (m, 1H), 4.39–4.61 (m, 2H), 4.24–4.37 (m, 1H), 3.55–4.14 (m, 5H), 3.14–3.26 (m, 3H) ppm. MS (+ESI) *m*/*z* 450 ($M+H^+$). Anal. Calcd for $C_{20}H_{18}F_3N_5O_2S{\cdot}2.65HCl{\cdot}1.35CH_3OH$: C, 43.60; H, 4.35; N, 11.77. Found: C, 43.51; H, 4.46; N, 11.88.

12. Harris, R. L. N. *Synthesis* **1980**, 841–842.
13. Hamilton, G. L.; Backes, B. J. *Tetrahedron Lett.* **2006**, *47*, 2229–2231.