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α-Heteroarylation of Esters, Lactones, Amides, and Lactams by Nucleophilic Aromatic Substitution

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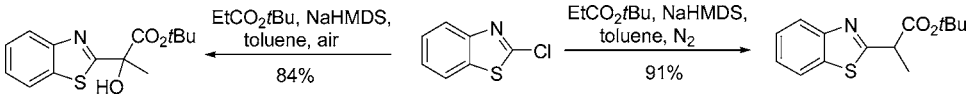
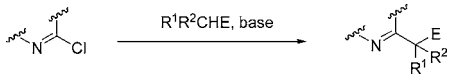
ABSTRACT



A mild and efficient α-heteroarylation of simple esters and amides was developed via nucleophilic aromatic substitution. The choice of NaHMDS in toluene gave the best results. A tandem α-heteroarylation and hydroxylation protocol using air as the oxidant afforded tertiary alcohols in good yields.

The α-arylation of carbonyl compounds is a useful reaction to prepare α-aryl acetic acids, esters, and amides which are common intermediates used in medicinal chemistry. These compounds are often prepared from one of several classical reactions that lack functional group compatibility and regiospecificity.[1] The most recent advance of such a reaction can be exemplified by the pioneering work of the Hartwig[2] and Buchwald[3] groups. They utilized the Pd-catalyzed α-arylation of carbonyl compounds with aryl halides, which are typically phenyl iodides or bromides. In contrast, heteroaryl halides, such as chlorides, are rarely utilized by this strategy.[4] Thus, it would be complimentary to develop a general procedure for α-heteroarylation of carbonyl compounds with heterocyclic halides, some of which are often unreactive toward Pd-catalyzed α-arylations. The $S_{RN}1$ approach[5,6] usually suffers from low yields, inconvenient procedures involving the handling of the ammonia solvent, and photostimulated conditions or the incompatibility of substrates with strong bases such as sodium amide. Alternatively, nucleophilic aromatic substitution (S_NAr) (Scheme 1) may present advantages. Previous reports of such transformations involving ester enolates are limited to doubly stabilized enolates such as malonates,[7] malonitriles,[7,8] ammonium ylide esters,[9] and α-iminoesters.[10] Herein, we report a mild and general protocol to prepare α-heteroaryl esters or amides using readily available heterocyclic chlorides and simple ester or amide enolates. To the best of our knowledge, this is the

Scheme 1



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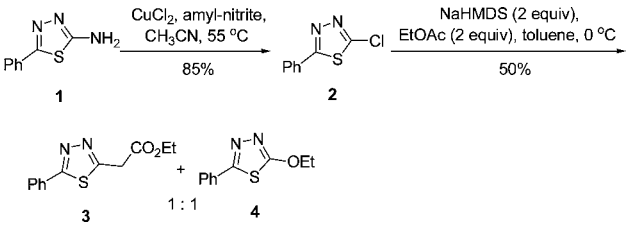
first report of a general and practical α-heteroarylation of simple esters or amides via the S_NAr reaction.

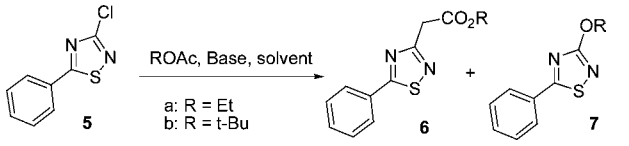
In a medicinal chemistry program, we attempted to synthesize 2-substituted 1,3,4-thiadiazol-5-ylacetic ester **3**. Instead of adopting a rather lengthy seven-step synthesis to access **3** as described in the literature,[11] we explored the possibility of a S_NAr route. Inspired by a recent publication on α-arylation of nitriles from Merck process chemists,[12] we applied the similar reaction conditions for a facile synthesis of α-thiadiazole acetate **3** (Scheme 2). When chlorothiadiazole **2** was reacted with ethyl acetate in the presence of NaHMDS, the desired product **3** was obtained, yet accompanied with side product **4** in a 1:1 ratio. The two-step synthesis rapidly provides **3** from commercially available aminothiadiazole **1** albeit in low yield. Starting with this reaction, we aimed at developing a general and practical approach to access α-heterocyclic esters and amides.

Scheme 2



Using substrate **5** as a model system,[13] we systematically investigated the impact of base, solvent, temperature, and reactant ratio on the reaction. The reaction condition optimization is summarized in Table 1. We again discovered byproduct **7a** when ethyl acetate was employed (Table 1, entry 1). Presumably, the treatment of ethyl acetate with base generates the enolate, which then undergoes a Claisen condensation to release ethoxide. The resulting ethoxide subsequently reacts with **5** to yield aryl ether **7a**. We then attempted the reaction at −78 °C to minimize the formation of aryl ether **7a**. However, overnight reaction at −78 °C gave low conversion (∼30%) of the starting material with 12% isolated yield of **6**, although the side reaction was indeed suppressed (Table 1, entry 2). Subsequent warming of the reaction mixture to 0 °C increased the yield of both **6** and **7a** as observed by LC/MS. Thus, it appears to be difficult to diminish the side reaction via temperature control while still driving the desirable reaction to completion. By switching ethyl acetate to *tert*-butyl acetate, we were pleased to see the improved yield (36%) of **6b** and no formation of **7b** (Table 1, entry 3). Meanwhile, about a 10% yield of bisarylated product was detected if the ratio of acetate, base, and **5** was 1:1:1. If the ratio of ester and base to **5** was increased to 3:3:1, 87% yield of **6b** was obtained and the bisarylated product was no longer detectable by LC/MS. The formation of aryl ether was completely eliminated most likely because of the sluggishness of the Claisen condensation to generate *tert*-butoxide. Furthermore, even if *tert*-butoxide is ever formed, the steric hindrance would presumably prevent its substitution with aryl halides. Now, using *tert*-butyl acetate as a substrate, we found that solvent plays a significant role in this reaction. The use of THF, dioxane, or diethyl ether gave poor yields of the desired product (Table 1, entries

Table 1. Effect of Base, Solvent, Temperature, and Reactant Ratio on the Reaction



entry[a]	base	*T* (°C)	reaction time/h	solvent	isolated yield of **6** (%)
1: R = Et	NaHMDS (0.6 M in toluene)	0	2	toluene	20 (40% of **7a**, 40% of **5**)
2: R = Et	NaHMDS	−78	16	toluene	12 (67% of **5**)
3[b]: R = *t*Bu	NaHMDS	0, rt	2, 16	toluene	36 (10% bisarylated product + 30% of **5**)
4: R = *t*Bu	**NaHMDS**	**−78, 0**	**0.5, 5**	**toluene**	**87**
5: R = *t*Bu	NaHMDS	0, rt	2, 16	dioxane	0
6: R = *t*Bu	NaHMDS	0, rt	2, 16	Et_2O	51
7: R = *t*Bu	NaHMDS	0, rt	2, 16	THF	<5
8[c]: R = *t*Bu	NaHMDS	0, rt	2, 16	THF	41
9: R = *t*Bu	**NaHMDS**	**0, rt**	**2, 16**	**toluene**	**85**
10: R = *t*Bu	LDA (0.5 M in THF)	0, rt	2, 16	toluene	<5
11: R = *t*Bu	NaH (60% in mineral oil)	0, rt	2, 16	toluene	43
12: R = *t*Bu	TMPLi (prepared in situ in THF)	0, rt	2, 16	toluene	32
13: R = *t*Bu	KHMDS (0.5 M in toluene)	0, rt	2, 16	toluene	49
14: R = *t*Bu	**LiHMDS (1 M in THF)**	**0, rt**	**2, 16**	**toluene**	**81**

[a] Procedure A: under N_2 to a solution of **5** (0.25 mmol) and acetate (0.75 mmol) in 1 mL of solvent was added base (0.75 mmol) at the indicated temperature. [b] 0.25 mmol of **5**, 0.25 mmol of *tert*-butyl acetate, and 0.25 mmol of base were used. [c] To a solution of acetate was added base at 0 °C. After being stirred for 30 min at 0 °C, to the resulting solution was then added **5**.

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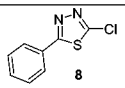
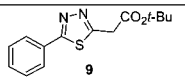
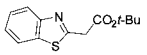
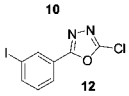
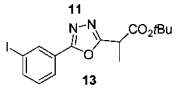
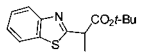
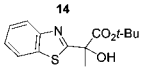
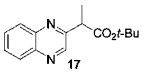
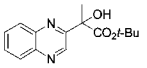
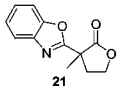
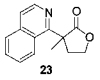
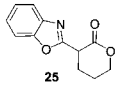
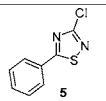
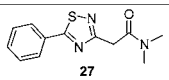
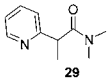
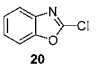
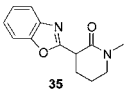
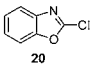
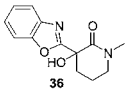
(13) Only 9% yield of the desired product was obtained for the reaction of ethyl acetate enolate with methyl chlorothiadiazole as recorded in the literature. Collins, I.; Moyers, C.; Davey, W. B.; Rowley, M.; Bromidge, F. A.; Quirk, K.; Atack, J. R.; McKerna, R. M.; Thompson, S.-A.; Wafford, K.; Dawson, G. R.; Pike, A.; Sohal, B.; Tsou, N. N.; Ball, R. G.; Castro, J. L. *J. Med. Chem.* **2002**, *45*, 1887−1900.

Table 2. Reaction Scope for Esters and Lactones[a]

entry	nucleophile	electrophile	product	yield (%)
1	$MeCO_2tBu$	 8	 9	79
2	$MeCO_2tBu$	 10	 11	84
3[b]	$EtCO_2tBu$	 12	 13	81
4[b]	$EtCO_2tBu$	 10	 14	91
5[c]	$EtCO_2tBu$	 10	 15	84
6[b]	$EtCO_2tBu$	 16	 17	92
7[c]	$EtCO_2tBu$	 16	 18	65
8[d]	 19	 20	 21	63
9[d]	 19	 22	 23	69
10[b]	 24	 20	 25	49
11	$EtCO_2tBu$	 26		0

[a] Following procedure A described in Table 1 unless otherwise noted. [b] 1 equiv of nucleophile, 2 equiv of base, and 1 equiv of chloride were used. [c] Procedure B: to the nucleophile (1 equiv) and halide (1 equiv) at 0 °C was added base (2 equiv) under N_2. After 2 h at room temperature, the reaction mixture was exposed to air and stirred for 12 h. [d] 1 equiv of nucleophile, 1 equiv of chloride, and 1.2 equiv of base were used.

Table 3. Reaction Scope for Amides and Lactams[a]

entry	nucleophile	electrophile	product	yield (%)
1	$MeCONMe_2$	 5	 27	69
2[b]	$EtCONMe_2$	 28	 29	71
3[b]	 30	 31	 32	81
4[b]	 30	 31	 33	77
5[b]	 34	 20	 35	89
6[b]	 34	 20	 36	63
7[b]	37	38	39	87
8[c]	40	41	42	70
9[d]	43	20	44	66 (d.r. 2:1)
10[e]	43	20	45	71 (d.r. 3:1)
11	$EtCONMe_2$	46		0

[a] Following procedure A described in Table 1 unless otherwise noted. [b] 1 equiv of nucleophile, 2 equiv of base, and 1 equiv of chloride were used. [c] Follow general procedure B of Table 2. To a nucleophile (1 equiv) and chloride (1 equiv) at 0 °C was added base (2 equiv) under N_2. After 2 h, the reaction mixture was warmed to room temperature and stirred for 12 h before it was exposed to air. [d] The enolate was formed by treating the amide (2 equiv) with base (2 equiv) at −78 °C and was stirred for 30 min prior to the addition of an electrophile (1 equiv) under nitrogen. [e] After following d, the reaction mixture was warmed to room temperature over 2 h and then exposed to air.

5−8). The major byproduct observed was the dechlorinated phenyl thiadiazole. Interestingly, when diethyl ether was employed, an appreciable amount of **6b** was isolated in contrast to THF and dioxane (Table 1, entry 6). Toluene is clearly a superior solvent in this reaction, and dechlorination was not observed despite a small amount of THF present in the commercial base solution (Table 1, entry 14). To avoid dechlorination in THF, one modification is to generate the enolate before the addition of heterocyclic halides (Table 1, entry 8). This procedure is less convenient than procedure **A** but does improve the yield dramatically. The choice of base also had a profound impact on the reaction. Sodium or lithium hexamethyldisilazide (Table 1, entries 9 and 14) gave much higher yields than their potassium counterpart (Table 1, entry 13). The worst case is LDA, which gave a complex reaction mixture with a trace amount of the desired product **6b** (Table 1, entry 10). Lithium tetramethylpiperidine (LTMP) gave a comparably modest yield as KHMDS (Table 1, entry 12).

We subsequently explored the scope of this reaction as shown in Tables 2 and 3. Various readily available chloroheterocycles including benzothiazole, oxadiazole, benzoxazole, quinoxaline, pyrazine, isoquinoline, pyridine, pyridazine, and 1,2,4- and 1,3,4-thiadiazoles were employed. The scope of nucleophiles extends to five- and six-membered lactones (Table 2, entries 8−10) and lactams (Table 3, entries 3−10). Known to be reactive toward the Pd-catalyzed α-arylations, the iodophenyl moiety remains intact under the nucleophilic aromatic substitution conditions (Table 2, entry 3) and offers an opportunity for further cross-coupling reactions. The formation of quaternary carbon atoms is possible as shown in entries 8 and 9 of Table 2. It was found

that δ-valerolactone **24** reacted more slowly compared to other substrates and gave a poorer yield of the desired product (Table 2, entry 10). Substrates such as chloropyrimidines (Table 2, entry 11 and Table 3, entry 11) or chloroimidazole (Table 3, entry 8) failed to give any α-arylation product.

Interestingly, when chlorobenzothiazole **10** was employed to react with *tert*-butyl propionate without rigorous exclusion of air, we observed two products corresponding to the desired α-benzothiazole ester **14** (49%) and tandem α-arylation and α-hydroxylation product **15** (39%).[14] When we carefully conducted the reaction under nitrogen, only **14** was obtained in 91% yield (Table 2, entry 4). On the other hand, if the reaction mixture was warmed to ambient temperature and then exposed to air, the hydroxylation product **15** was formed exclusively (Table 2, entry 5). Thus, this one-pot protocol provides an inexpensive, convenient, and efficient approach to access α-hydroxy-α-heteroaryl esters[15] compared to the conventional methods, such as the use of Vedejs' reagent,[16] Rubottom oxidation,[17] or Davis oxaziridine.[18] Furthermore, this procedure also applies to amides and lactams, as shown in entries 4, 6, and 10 in Table 3. The reaction of oxindole and chloroimidazole (Table 3, entry 8) failed to give the α-arylation product after 12 h. When the reaction was exposed to air afterward, the hydroxy product **42** was isolated in good yield indicating that the enolate was indeed formed and subsequently oxidized by air.

The attempt to establish asymmetric stereoinduction using Meyers' auxiliary[19] did not give high diastereoselectivity. This is most likely due to the racemization of the product (Table 3, entry 9) because the α-proton of the product **44** is more acidic than that of the starting material **43**.

In conclusion, we have developed an efficient and rather general protocol for the α-heteroarylation of simple esters, lactones, amides, and lactams by nucleophilic aromatic substitution. This method provides several desirable features that are either complementary or improvements to the Pd-catalyzed reactions. Specifically, heteroaryl chlorides may be used, which are more commercially available, much more stable, and/or cheaper than the corresponding bromides or iodides. Reactions can also be conducted at ambient temperature as opposed to the elevated temperature usually required by Pd-catalyzed α-arylations. Last, the introduction of air to the reaction leads to α-hydroxy-α-heteroaryl esters and amides offering more diversity to this process.

Acknowledgment. We thank Drs. Artis Klapars, Cheng-yi Chen, and James R. Tata for helpful discussions.

Supporting Information Available: Representative experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Most likely, the anion is oxidized through a radical aerobic oxidation mechanism: (a) Nobe, Y.; Arayama, K.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 18006−18007 and references therein. (b) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, *16*, 1731−1734. (c) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578−1591.

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