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Dealkylative functionalization of tertiary amines with electron deficient heteroaryl chlorides

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Abstract—The selective dealkylative arylation of trialkyl amines, *N*-alkyl pyrrolidines, *N*-alkyl piperidines and dialkyl anilines with electron deficient heteroaryl chlorides was investigated. Efficient and practical reaction conditions were determined for a range of substrates.

During the course of our research in the metabolic disease area, *N*-aryl or *N*-heteroaryl pyrrolidines were developed as leads for promising development targets. Fortuitously, powerful and mild synthetic methods such as dipolar additions employing azomethine ylides[1] can give access to pyrrolidines that are decorated with a range of substituents and functional groups. However, these methods often leave products with an undesired methyl or benzyl group on the nitrogen. On occasions, our efforts to remove these nitrogen substituents to provide substrates for nucleophilic aromatic substitution chemistry or metal-mediated cross-couplings met with limited success due to the presence of sensitive functionality displayed upon the pyrrolidine. For example, the reductive removal of *N*-benzyl groups can be difficult in the presence of aryl halides or nitro groups.[2] The use of chloroformates to quaternize and dealkylate the pyrrolidine nitrogen to give carbamates for subsequent deprotection worked moderately well for some substrates.[3] However, the efficiency of this process was very much dependent on the nature of the amine.[4]

By analogy to the aforementioned chloroformate-mediated process, we were curious whether *N*-alkyl pyrrolidines could be directly substituted with aryl and heteroaryl halides to provide *N*-aryl and *N*-heteroaryl pyrrolidines in a single step (Fig. 1). Reports detailing useful applications of this transformation are limited,

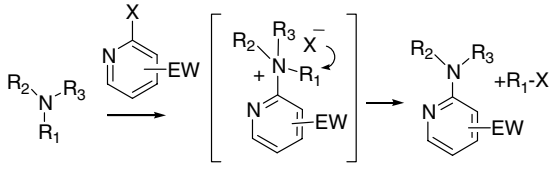

Figure 1. Quaternization of 3° amines with electron deficient heteroaromatic halides and dealkylation.

and have focused on the reactions of triazinyl,[5] pyrimidinyl and quinazolinyl chloride substrates[6] with simple 3° amines. Attempts to extend these methods to a wider range of heteroaryl chloride electrophiles has required the use of high pressures and reaction times that extend over days.[7] Here we report our efforts to identify reactivity trends and practical reaction conditions to make this transformation a viable option for a wide range of substrates.

An early report detailing the substitution of 2,4,6-trichlorotriazine with 3° amines at high temperatures identified over-addition as a major side product.[5] Accordingly, **1**,[8] for which over-addition is not an issue, was chosen to explore this transformation in more detail (Table 1). Treatment of **1** (1.2 equiv) with *N*-methylpiperidine (0.5 M in CH_3CN) at 22 °C resulted in a near quantitative yield of **2a** (98%) after 12 h. *N*-Benzyl- and *N*-ethylpiperidine reacted more slowly and required heating (60 °C) to give complete conversion to **2a** in 96%, and 98% yield, respectively. The reactivity trend for *N*-substituents (Me > Bn) is the opposite of that

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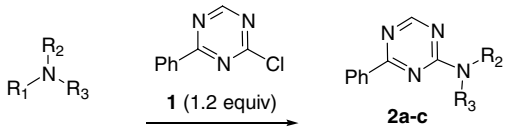
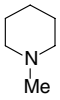
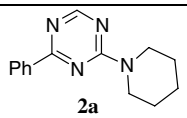
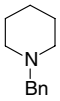
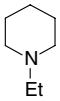
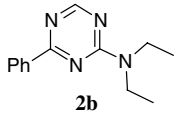
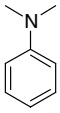
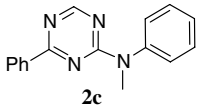
Table 1. Triazinyl chloride **1** reaction with amines and aniline



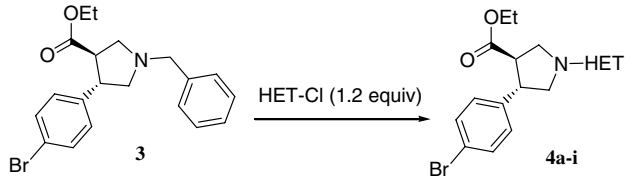
Entry	$R_1NR_2R_3$	Product	Yield[a]
1		 **2a**	98[b]
2		**2a**	79[b] (96)[c]
3		**2a**	71[b] (98)[c]
4		 **2b**	92[b]
5		 **2c**	96[d]

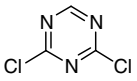
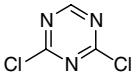
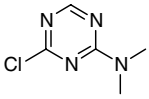
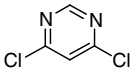
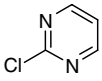
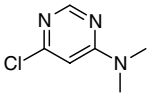
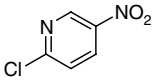
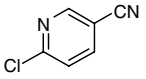
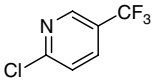
[a] Yields of analytically pure material based upon amine equivalent.
[b] Conditions: CH_3CN (0.5 M), 22 °C, 12 h.
[c] Conditions: CH_3CN (0.5 M), 60 °C, 3 h.
[d] Conditions: CH_3CN (0.5 M), 80 °C, 12 h.

observed for the quaternization and dealkylation of 3° amines with chloroformates.[9] These results may suggest that for dealkylative substitution with heteroaryl chlorides, reversible quaternization is the rate-limiting step with the reactivity profile reflecting the steric availability of the nitrogen lone pairs. Triethylamine substitution of **1** occurred at room temperature to give **2b** in 92% yield while less nucleophilic aniline required more forcing conditions (80 °C) to give **2c** (96%).

A representative substrate, pyrrolidine **3,** was employed to examine the reactivity of several heteroaryl chloride partners (Table 2). Reaction of **1** (1.2 equiv) with **3** (0.2 M in CH_3CN) at 22 °C gave **4a** in 86% yield.[10] Treatment of 2,6-dichlorotriazine with **3** under similar conditions resulted in a poor yield of **4b** due to the formation of a significant amount of di-addition product **6** (Fig. 2). The use of lower reaction temperatures or solvents of varying character did not improve this result. It is likely that intermediate **5** is more reactive to substitution than is 2,6-dichlorotriazine, and that a second addition of **3** competes with dealkylation. It is doubtful that the formation of **6** is due to a second addition to **4b**, due to the reduced reactivity of amine-substituted chlorotriazines. This is evident since the reaction of (*N*,*N*-dimethyl)amino-chlorotriazine and **3** required the use of more forcing conditions (80 °C, 0.5 M CH_3CN, 7 h) to provide **4c** in 80% yield. We hypothesized that the yield of **4b** could be improved with the inclusion of a chloride ion source to increase the rate of dealkylation of **5** versus the rate of addition of a second equivalent of **3**. After

Table 2. Treatment of **3** with various heteroaromatic chlorides



Entry	HET-Cl	Prod	Conditions	Yield[a]
1	**1**	**4a**	22 °C, 2 h, CH_3CN[b]	86
2		**4b**	22 °C, 1 h, THF[b]	45[c]
3		**4b**	22 °C, 1 h, 0.25 M LiCl THF[b]	96
4		**4c**	80 °C, 7 h, CH_3CN[d]	80
5		**4d**	150 °C (μW), 0.5 h, CH_3CN[e]	85
6		**4e**	200 °C (μW), 0.5 h, NMP[e]	68
7		**4f**	220 °C (μW), 0.5 h, NMP[e]	Trace
8		**4g**	180 °C (μW), 0.5 h, NMP[e]	80
9		**4h**	220 °C (μW), 0.5 h, NMP[e]	58
10		**4i**	220 °C (μW), 0.5 h, NMP[e]	16

[a] Yields of analytically pure material based upon amine equivalent.
[b] Reaction performed at 0.2 M in **3**.
[c] Di-addition gave **6** (16%) as a side product (Fig. 2).
[d] Reaction performed at 0.4 M in **3**.
[e] Reaction performed at 2 M in **3**.

profiling a number of such reagents, LiCl (0.25 M) in THF was found to dramatically reduce the formation of **6** to give **4b** in 96% yield.[11]

Previous reports employed high reaction pressures and multi-day reaction times to expand the scope of this transformation.[7] We found that microwave-assisted synthesis provided practical reaction conditions for a range of substrates.[12] Treatment of 4,6-dichloropyrimidine with **3** (2 M in CH_3CN, 150 °C, 0.5 h) gave **4d** in 80% yield. Unlike the disubstitution that was observed for 2,6-dichlorotriazine (entry 2) substitution, over-addition to 4,6-dichloropyrimidine was presumably not observed because the quaternized intermediate formed is short-

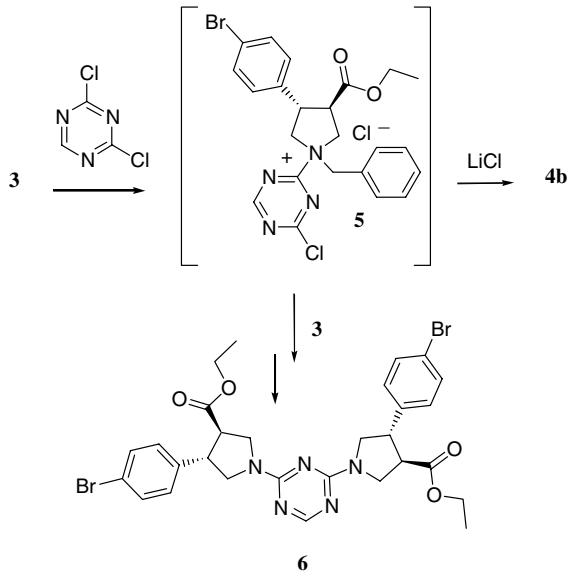


Figure 2. LiCl suppresses di-addition to activated **5**.

lived at 150 °C. Pyrimidines substituted with chlorine at the less reactive 2-position reacted with **3** at 200 °C to give **4e** (68%). The substitution of more electron-rich amine-substituted pyrimidines was unsuccessful, even at high temperatures (entry 7). Pyridines with electron-withdrawing groups in the 4-position served as viable substrates (entries 8–10). In the case of 2-chloro-4-nitropyridine, substitution with **3** gave at 180 °C **4g** (80%), and the substitution of 2-chloro-4-cyanopyridine at 220 °C gave **4h** (58%). Finally, the reaction of **3** with 2-chloro-4-trifluoromethylpyridine at 220 °C provided a low yield of **4i** (16%) suggesting that inductive stabilization of the quaternized intermediates is less productive than resonance stabilization and defining a reactivity limit for pyrimidines using our methods.

In conclusion, the dealkylative arylation of sensitive 3° amine substrates with electron-poor heteroaryl chlorides is shown to be an effective strategy to prepare a variety of compounds. In addition, reactivity profiles of a number of electron-poor heteroaryl chlorides and 3° amine substituents were determined. Further applications of this practical and efficient method will be reported in due course.

Acknowledgements

The authors thank Jan Waters for technical assistance in the final analytical characterization of reaction products. G.L.H. thanks the Abbott Summer Internship Program for sponsorship.

Supplementary data

Supplementary data including analytical data for **2a–c**, **3**, **4a–e**, **4g–h** and **6** is available online with this article and can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.104.

References and notes

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2. Green, T. W.; Wuts, P. G. M. *Protective groups in Organic Synthesis*, 2nd ed.; Wiley and Sons: New York, 1991, pp 364–365.
3. For a review detailing with the reactions of 3° amines with acid chlorides and chloroformates see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1–7.
4. The forcing conditions that were often needed to achieve a reasonable level of conversion decomposed the chloroformate and resulted in an increase in the acidity of the reaction media. In turn, substrates bearing acid sensitive groups such as Boc-protected amines decomposed.
5. Kober, E.; Ratz, R. *J. Org. Chem.* **1962**, *27*, 2509–2514.
6. Yoshida, K.; Taguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 919–922.
7. Matsumoto, K.; Hashimoto, S.; Otani, S. *J. Chem. Soc., Chem. Commun.* **1991**, 306–307.
8. Harris, R. L. *Synthesis* **1980**, 841–842.
9. For chloroformates, quaternization of 3° amines is relatively fast, with the rates of dealkylation governing the observed reactivity profiles: Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233–3236.
10. Pyrrolidine substrates that feature acid labile functionalities such as Boc-protected amines were viable substrates for this transformation, even when forcing conditions were employed. Unpublished results.
11. It is possible that more reactive heteroaryl chlorides such as 2,6-dichlorotriazine may shift the rate-limiting step to dealkylation accounting for these observations. However, the addition of LiCl in this transformation did not dramatically increase the overall rate of the reaction and suggests that quaternization is still rate limiting.
12. *Representative procedure* (**4d**). To 4,6-dichloropyrimidine (72 mg, 0.48 mmol) was added **3** (160 mg, 0.40 mmol) as a solution in CH_3CN (0.2 mL). The reaction mixture was submitted to microwave irradiation for 30 min at 150 °C, concentrated and purified over silica gel (EtOAc/hexanes, 0:100–30:70 gradient) to give 4 d (140 mg, 85%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.48 (d, $J = 8.3$ Hz, 2H), 7.16 (d, $J = 8.3$ Hz, 2H), 6.33 (s, 1H), 4.13 (q, $J = 7.3$ Hz, 2H), 4.00–4.10 (m, 1H) 3.74–3.80 (m, 2H), 3.40–3.60 (m, 2H), 3.20–3.25 (m, 1H), 1.19 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 171.3, 160.3, 159.5, 158.1, 137.8, 131.9, 128.9, 121.4, 101.9, 61.3, 52.6, 49.8, 49.5, 46.5, 14.0. Anal. Calcd for $C_{17}H_{17}BrClN_3O_2$: C, 49.72; H, 4.17; N, 10.23. Found: C, 49.80; H, 3.89; N, 10.07.