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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1527–1529

Synthesis of 4-(cyclic dialkylamino)-7-azaindoles by microwave heating of 4-halo-7-azaindoles and cyclic secondary amines

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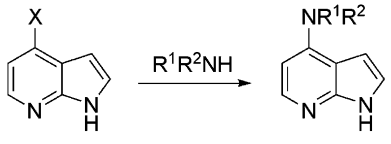
Received 5 December 2006; revised 20 December 2006; accepted 4 January 2007
Available online 7 January 2007

Abstract—Nucleophilic aromatic substitution of 4-chloro- and 4-fluoro-7-azaindoles with cyclic secondary amines under microwave heating gave a straightforward and rapid synthesis of 4-(cyclic dialkylamino)-7-azaindoles. 4-Fluoro-7-azaindoles showed a greater reactivity towards S_NAr reactions under these conditions than 4-chloro-7-azaindole.

1. Introduction

Many compounds of potential pharmaceutical interest contain the 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine) motif,[1–6] including examples of simple 4-*N*- or 4-*O*-substituted compounds.[4,7,8] As part of a drug discovery research program, we required a method for the preparation of 4-(cyclic dialkylamino)-7-azaindoles. The most direct route, involving the nucleophilic aromatic substitution of a 4-halo-7-azaindole with appropriate amines (Scheme 1), has received only sporadic attention and requires quite drastic reaction conditions.[9,10] For example, heating a neat mixture of 4-chloro-7-azaindole **1**[9] with a five-fold excess of dimethylamine hydrochloride or other simple dialkylamines at 180 °C provided the nucleophilic displacement products.[9,10] However, similar conditions using primary alkylamines or anilines gave only the 4-amino-5-azaindole (1*H*-pyrrolo[3,2-*c*]-pyridine) products of displacement–rearrangement.[9]



1 X = Cl
2 X = F

Scheme 1.

Recently, palladium-catalysed cross-coupling of **1** and primary anilines has been demonstrated, leading to good yields of 4-anilino-7-azaindoles.[11] A similar cross-coupling of allylamine with **1** has also been reported.[12]

Improvements in reactivity are commonly seen for S_NAr reactions when a fluoride leaving group is employed in the place of a chloride.[13] The rate determining step of the S_NAr mechanism is the initial addition of the nucleophile to the aromatic carbon, and the greater electronegativity of fluorine relative to chlorine accelerates this by increasing the positive charge on the reactive aromatic carbon. A concise synthesis of 4-fluoro-7-azaindole **2** has been described,[12] and we therefore chose to compare the reactivity of 4-chloro- and 4-fluoro-7-azaindoles **1** and **2**. We anticipated that high temperatures might still be necessary and thus looked to microwave heating as a convenient means of achieving this, which was also compatible with a parallel synthesis approach.[14] The benefits of microwave heating for accelerating thermal S_NAr reactions of heteroaromatic halides has been demonstrated.[15–18]

2. Results and discussion

4-Chloro-7-azaindole **1** was prepared from 7-azaindole by the literature procedure.[10] To obtain 4-fluoro-7-azaindole **2** we initially used a modification of the published methodology[12] (Scheme 2), obtaining 1-triisopropyl-4-bromo-7-azaindole **3** in 3 steps from 7-azaindole. While the original procedure for conversion of **3** to

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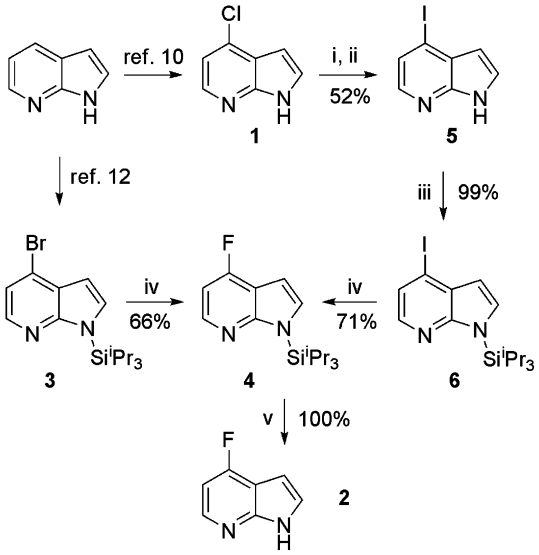
doi:10.1016/j.tetlet.2007.01.003



Scheme 2. Reagents and conditions: (i) AcCl, NaI, MeCN, reflux; (ii) 2 M NaOH, THF, 40 °C; (iii) NaH, TIPSCl, THF, reflux; (iv) *n*-BuLi, Et_2O, −78 °C then $FN(SO_2Ph)_2$, THF, −78 °C; and (v) TBAF, THF, rt.

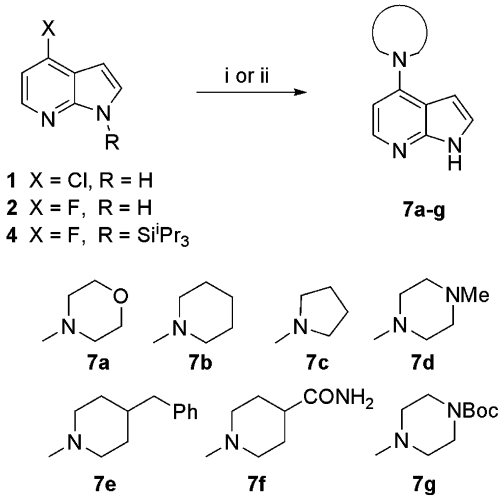
fluoride **4** involved reaction with *tert*-butyllithium, we found that this reagent could be replaced with *n*-butyllithium provided the lithiation step was carried out in diethyl ether, to give **4** in a comparable yield (66%). The use of THF as the solvent gave no metalation, although this solvent was required for the addition of the electrophilic fluorine source (*N*-fluorobenzenesulfonimide) which was otherwise insoluble in diethyl ether. The synthesis of **4** and **2** via the 4-iodo derivative **6** was also investigated. Trans-halogenation[19,20] of **1** was achieved using sodium iodide and acetyl chloride to generate 4-iodo-7-azaindole **5**[21] after hydrolysis of the *N*-acetylated intermediate. Protection of **5** as the *N*-triisopropylsilyl derivative **6** was followed by metalation with *n*-butyllithium and quenching with *N*-fluorobenzenesulfonimide to give **4**. The yield of this transformation was similar to that starting from the corresponding bromide. The synthesis of **4** and **2** via iodide **6** provides an alternative route to these interesting synthetic intermediates.[12,22]

The temperature dependence of the reactions of **1** and **2** with excess morpholine under microwave irradiation was investigated (Table 1). In both cases, the desired 4-morpholino substitution product **7a** was formed. The 4-fluoro substrate **2** showed a moderate enhanced reactivity over chloride **1**. It is therefore possible that use of the fluoride would be beneficial for the reactions of more complex, temperature sensitive amines. It is noteworthy that 4-fluoro-7-azaindole **2** is more stable and less reactive to substitution than 4-fluoropyridine,[23] presumably as a result of the presence of the fused electron-rich pyrrole ring in the bicycle. The lowest temperatures that gave >95% reaction in 2–3 h were chosen for each substrate (**1**: 180 °C, 3 h; **2** and **4**: 160 °C, 2 h) and a range of simple cyclic secondary amines were investigated (Scheme 3, Table 2). The behaviour of the silyl-protected intermediate **4** was studied since the high temperatures and generation of fluoride ion during the substitution reaction were anticipated to give concomitant *N*-desilylation.

Table 1. Temperature dependence of the reaction of **1** and **2** with morpholine[a]

Temperature[b] (°C)	Time[c] (h) for complete conversion to **7a**	
	1, X = Cl	**2**, X = F
120	n.d.[d]	12
140	n.d.	4.5
160	7	2.0
180	2.5	1.5

[a] Compound **1** or **2**, morpholine (5 equiv), Et_3N (5 equiv), NMP (0.4 M).
[b] Internal reaction vessel temperature (Biotage Initiator 60 microwave reactor).
[c] Time required for >95% conversion of **1** or **2** as determined by HPLC analysis of the reaction mixture at 30 min intervals.
[d] n.d. = not determined.



Scheme 3. Reagents and conditions: (i) **1**, amine (5 equiv), Et_3N (5 equiv), NMP, microwave 180 °C, 3 h; and (ii) **2** or **4**, amine (5 equiv), Et_3N (5 equiv), NMP, microwave 160 °C, 2 h.

Table 2. S_NAr reactions of **1**, **2** and **4** with cyclic secondary amines under the conditions shown in Scheme 3

Product	Yield[a] from		
	1	**2**	**4**
7a	59 (57[b])	61[c]	56[d]
7b	53[e]	61	56
7c	65	63	74
7d	65	43	55
7e	62	43	59 (32[d])
7f	54	51	n.d.[f]
7g	n.d.	n.d.	20 (24[d])

[a] Isolated yields of purified material homogeneous by ^1H NMR and HPLC analysis (>95%).
[b] Et_3N omitted.
[c] 6 equiv of amine used.
[d] 2 equiv of amine used.
[e] 4 h reaction time.
[f] n.d. = not determined.

In most cases, moderate to good yields of the required 4-amino-7-azaindoles **7a**–**g** were obtained after ion exchange and/or chromatographic purification. Substituted piperidines, pyrrolidine and less nucleophilic cyclic amines such as morpholine and *N*-methylpiperazine were effectively incorporated. No significant differences were observed in the yields for conversion of **1**, **2** or **4**, but lower temperature and shorter reaction times were adequate for the reaction of fluorides **2** and **4**. In the case of the reaction of morpholine with **4**, a good yield of **7a** was obtained using only 2 equiv of the amine. However, this did not translate to the reaction of 4-benzylpiperidine to give **7e**, where 5 equiv of the amine were necessary. The reaction of **1** with morpholine was unaffected by the inclusion or omission of triethylamine. The reaction of Boc-protected piperazine with **4** was attempted to investigate if the method was compatible with this temperature-labile protecting group, and low but reproducible yields of the *N*-Boc-protected 4-piperazinyl-7-azaindole were obtained. Although compounds **7a**–**g** are structurally simple, with the exception of **7g**[24] this is to our knowledge the first time their synthesis has been described.

In conclusion, a straightforward and rapid synthesis of 4-(cyclic dialkyl)amino-7-azaindoles was demonstrated through the displacement of 4-chloro and 4-fluoro leaving groups with cyclic secondary amines under microwave heating. An alternative synthesis of 4-fluoro-7-azaindole was developed based on the transhalogenation of 4-chloro-7-azaindole to 4-iodo-7-azaindole and subsequent metalation–electrophilic fluorination.

3. Representative experimental procedure

A solution of **2** (0.020 g, 0.153 mmol), morpholine (0.080 mL, 0.915 mmol) and Et_3N (0.128 mL, 0.915 mmol) in NMP (0.5 mL) was heated in a Biotage Initiator 60 microwave reactor at 160 °C for 2 h. Purification by ion exchange on an SCX-2 Isolute column, eluting with MeOH then 2 M NH_3–MeOH, followed by preparative TLC (EtOAc) gave **7a** (0.019 g, 0.094 mmol, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.48–3.50 (4H, m), 3.93–3.95 (4H, m), 6.46 (1H, d, J 5.5 Hz), 6.49 (1H, d, J 3.5 Hz), 7.22 (1H, d, J 3.5 Hz), 8.15 (1H, d, J 5.5 Hz), 10.40 (1H, br, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.7, 66.8, 100.1, 101.8, 110.5, 121.9, 144.1, 150.1, 151.7; m/z (ES+) 204 ($M+H^+$).

Acknowledgements

We thank Dr. T. McHardy for preliminary experiments on the reactivity of **1**. This work was supported by Cancer Research UK [CUK] Grant No. C309/A2187. Additional funding was received from Astex Therapeutics Ltd (J.J.C.).

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