Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 4249–4251
Tetrahedron Letters

Hydrogen peroxide promoted hydroxylation of haloarenes and heteroarenes

William R. Cantrell, Jr., William E. Bauta* and Tracy Engles

Genzyme Corporation, Therapeutics Manufacturing and Development, 14805 Omicron Drive, San Antonio, TX 78245, USA

Received 15 March 2006; revised 3 April 2006; accepted 6 April 2006

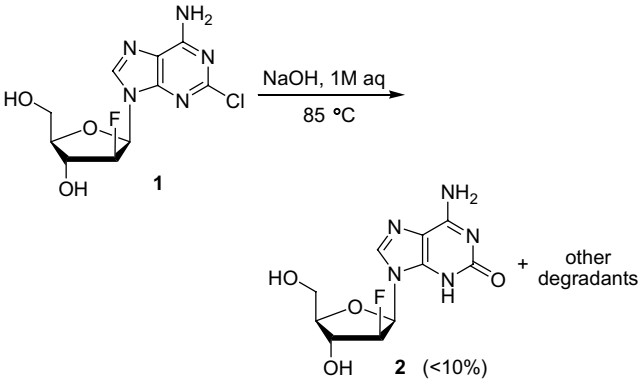
Abstract—Addition of aqueous hydrogen peroxide significantly accelerates the substitution reactions of hydroxide salts with haloarenes bearing electron withdrawing substituents. A similar effect is observed in the reactions of hydroxide salts with halogenated heteroarenes. Reactions are carried out in water or water–THF at ambient temperature or at 50–60 °C.

1. Introduction

Displacement of halogens by hydroxide anion on aromatic and heteroaromatic rings is often a difficult transformation.[1] Even in the case of haloarenes which are predisposed to S_NAr reactivity by the presence of strongly electron withdrawing functionalities, forcing conditions are generally required. Alternatives to hydroxide in such reactions have been developed, for example, by use of 2-butyn-1-ol,[2] 2-(methylsulfonyl)ethanol,[3] or sodium trimethylsilanoate.[4] Palladium catalyzed reactions to form *t*-butyl-aryl ethers have also been developed.[5] These *t*-butyl-aryl ethers can be readily cleaved to the corresponding phenols.

2. Results and discussion

During the course of our studies on the alkaline degradation of clofarabine (**1**), we observed conversion to a number of degradants upon prolonged heating with aqueous sodium hydroxide. One of these degradants, the isoguanine nucleoside (**2**), resulting from formal S_NAr reaction, was only produced as a small proportion of the mixture (Scheme 1). A review of the literature revealed a previous report by Raić-Malić and co-workers, where 2-fluoro-9*H*-purine-6-thiol derivatives were converted to the corresponding xanthines by the action of hydrogen peroxide in dilute ammonium hydroxide at room temperature.[6] Thus a formal double S_NAr displacement on the 2 and 6 positions of the purine ring had been achieved. However, when these reaction conditions were attempted with clofarabine (**1**), no significant production of **2** was observed. This result was not entirely unexpected, given the very high reactivity of 2-fluoropurines in comparison with other halopurines.[7] Also, Heller and Weiler had reported on the hydrogen peroxide accelerated displacement of nitro groups from *ortho*- and *para*-dinitrobenzenes to the corresponding phenols with sodium hydroxide in aqueous dioxane.[8] Aryl hydroperoxide intermediates were detected in these reactions. We thus decided to study hydrogen peroxide-promoted S_NAr reactions in selected aromatic



Scheme 1. Base degradation of clofarabine.

Keywords: Accelerated S_NAr; Mild conditions.
* Corresponding author. Tel.: +1 210 949 8481; fax: +1 210 949 8649; e-mail: william.bauta@genzyme.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.020

and heteroaromatic systems under various reaction conditions.

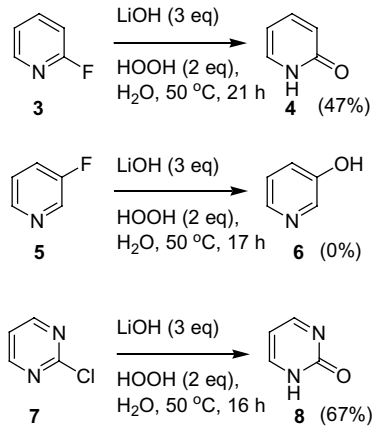
An aqueous suspension of clofarabine was treated with lithium hydroxide (3 mol equiv) and hydrogen peroxide (2 mol equiv) with vigorous stirring. After 17 h at room temperature, HPLC analysis showed 29% conversion to **2**. The mixture was heated to 60 °C for 5 h, whereupon the reaction was 86% complete by HPLC analysis. Workup and isolation afforded nucleoside **2** in 48% yield. Interestingly, use of catalytic (0.11 equiv) hydrogen peroxide led to a low (6.8%) conversion to **2**. Thus, a reactivity enhancement had been observed by addition of hydrogen peroxide.

The conversion of 4-nitrofluorobenzene to 4-nitrophenol has been accomplished using various methods.[2–4,9] We found that the reaction could be carried out with LiOH (3 equiv) and HOOH (2 equiv) in THF–water (Table 1, entry 1). Alternatively, a biphasic mixture of water and toluene could be used (entry 2), or in water alone (entry 3). Sodium hydroxide worked well in water (entry 4) but both sodium and potassium hydroxide afforded lower yield and conversion in THF–water (entries 4–6). Consistent with the clofarabine result, ammonium hydroxide gave low conversion (entry 7). As a control, the reaction proceeded to only 3% conversion in the absence of hydrogen peroxide (entry 8).

2-Nitrofluorobenzene reacted smoothly to 2-nitrophenol (entry 9) but 3-nitrofluorobenzene failed to react (entry 10). 2-Chloro and 4-chloronitrobenzene were unreactive under our usual reaction conditions but also when DMSO was used as a co-solvent (entries 11–12). Highly reactive 1-chloro-2,4-dinitrobenzene proceeded within 20 min to high conversion, affording the corresponding phenol (entry 13).

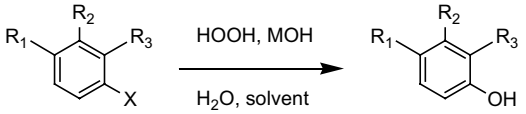
Mąkosza and Sienkiewicz have reported the vicarious nucleophilic substitution reactions of electron deficient aromatic systems with *t*-butyl hydroperoxide in liquid ammonia.[9] While these authors observed S_NAr substitution in the case of 4-fluoronitrobenzene, vicarious nucleophilic substitution products resulted with 3-fluoronitrobenzene, 3-chloronitrobenzene, and 1,3-dinitrobenzene (entry 14). Under our conditions we observed no reaction.

Some π-deficient heterocyclic systems were investigated (Scheme 2). 2-Fluoro pyridine (**3**) reacted to afford 2-pyridone (**4**) in 47% yield (82% conv).[10] But 3-fluoro-



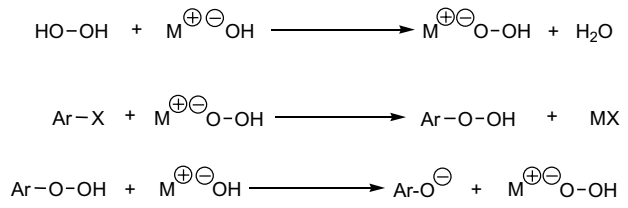
Scheme 2. Reactions of other halo heteroarenes.

Table 1. Hydrogen peroxide-promoted S_NAr reactions of haloaromatic compounds



Entry	R_1	R_2	R_3	X	M	Solvent	Conv[a] (%)	Yield[b] (%)
1	NO_2	H	H	F	Li	THF–H_2O	99	76
2	NO_2	H	H	F	Li	PhMe–H_2O	n.d.[c]	52
3	NO_2	H	H	F	Li	H_2O	98	60
4	NO_2	H	H	F	Na	H_2O	93	59
5	NO_2	H	H	F	Na	THF–H_2O	35	19
6	NO_2	H	H	F	K	THF–H_2O	52	28
7	NO_2	H	H	F	NH_4	H_2O	2	n.i.[d]
8	NO_2	H	H	F	Li	THF–H_2O	3[e]	n.i.
9	H	H	NO_2	F	Li	H_2O	90	57
10	H	NO_2	H	F	Li	H_2O	0	n.i.
11	NO_2	H	H	Cl	Li	DMSO–H_2O	Trace	n.i.
12	H	H	NO_2	Cl	Li	DMSO–H_2O	Trace	n.i.
13	NO_2	H	NO_2	Cl	Li	THF–H_2O	98	73
14	NO_2	H	NO_2	H	Li	THF	0	n.i.

[a] HPLC conversion.
[b] Isolated yield.
[c] Not determined.
[d] Not isolated.
[e] No H_2O_2 added.



Scheme 3. Proposed mechanism for hydrogen peroxide-promoted hydroxylation.

pyridine (**5**), was unreactive.[11] Under similar conditions, 2-chloropyrimidine (**7**) afforded 2-pyrimidone (**8**) in 67% yield (100% conv).[12]

A possible mechanism for hydrogen peroxide-promoted S_NAr reactions is outlined in Scheme 3. In the presence of hydroxide, hydrogen peroxide is converted to the more reactive hydrogen peroxide anion[13] and displaces the halogen to generate an intermediate aryl hydroperoxide, which further reacts with hydroxide to regenerate the peroxide anion and the desired product. We did not detect the aryl hydroperoxides by HPLC during the course of our study and did not see evidence for the formation of diarylhydroperoxide products, which would result from condensation of the aryl hydroperoxide anion with the haloarene. According to this mechanism, the reaction can be catalytic in hydrogen peroxide. However, we did not find this to be practical, probably owing to the modest stability of hydrogen peroxide under the reaction conditions.

3. Conclusion

In summary, we have demonstrated that aqueous hydrogen peroxide promotes the S_NAr reactions of hydroxide salts with various electron deficient aromatic and heteroaromatic systems under mild reaction conditions. These reactions were generally clean and not accompanied by vicarious nucleophilic substitution products.

A representative procedure is as follows. A 50 mL flask was charged with clofarabine (**1**, 0.352 g, 1.159 mmol), H_2O (6 mL), LiOH (0.083 g, 3.48 mmol), and H_2O_2 (30 wt %, 0.24 mL, 2.32 mmol). The mixture was stirred at 60 °C for 24 h. HPLC analysis showed 88% conversion. The reaction was worked up. A solution of $Na_2S_2O_3$ in H_2O was added until the peroxide test (starch–iodide paper) was negative. Acetic acid was added until the pH was 4–5. The volatiles were removed under vacuum. The residue was purified by reverse phase preparative HPLC chromatography (Waters Atlantis C_{18} OBD, 5 μm, 19 × 100 mm, 95% H_2O, 5% MeCN (v/v), isocratic) to give **2** as a white solid (0.16 g, 0.56 mmol, 48% yield). Mp = 292 °C (dec). ^{1}H NMR (DMSO-d_6) 10.74 (br s, 1H), 7.84 (1H, d, $J = 2.2$ Hz), 7.80 (br s, 2H), 6.13 (1H, dd, $J = 4.2$, 15.6 Hz), 5.93 (1H d, $J = 5.1$ Hz), 5.09 (1H, dt, $J = 3.9$, 52.5 Hz), 5.13 (1H, br s), 4.35 (1H, ddd, $J = 4.8$, 8.4, 18.7 Hz), 3.79 (1H, q, $J = 4.6$ Hz), 3.80–3.56 (2H, m). IR (KBr) 3371s br, 1675s, 1643s, 1606s, 1519w, 1379m, 1094m cm^{-1}. UV (H_2O/MeOH) λ_{max_1} 246.9 nm, λ_{max_2} 291.7 nm. Mass spec. (electrospray, positive) m/e $[M+H]^+ = 287$. Anal. Calcd for $C_{10}H_{12}FN_5O_4$: C, 42.11; H, 4.24; F, 6.66; N, 24.55. Found: C, 41.96; H, 4.00; F, 6.43; N, 24.57.

Acknowledgements

The authors thank Dr. Jim Goebel, for mass spectral data and useful discussions. We also thank Dr. Phil Bauer, for his support and advice.

References and notes

1. Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley Inter-Science: NY, 2001, p 861.2.
2. Levin, J. I.; Du, M. T. *Synth. Commun.* **2002**, *32*, 1401–1406.
3. Rogers, J. F.; Green, D. M. *Tetrahedron Lett.* **2002**, *43*, 3585–3587.
4. Krapcho, A. P.; Waterhouse, D. *Synth. Commun.* **1998**, *28*, 3415–3422.
5. (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225; (b) Parrish, C. A.; Buchwald, S. A. *J. Org. Chem.* **2001**, *66*, 2498–2500.
6. Prekupec, S.; Svedružić, D.; Gazivoda, T.; Mrvoš-Sermek, D.; Nagl, A.; Grdiša, M.; Pavelić, K.; Balzarini, J.; De Clerq, E.; Folkers, G.; Scapozza, L.; Mintas, M.; Raić-Malić, S. *J. Med. Chem.* **2003**, *46*, 5763–5772.
7. Gester, J. F.; Robins, R. K. *J. Org. Chem.* **1966**, *31*, 3258–3262.
8. Heller, R. A.; Weiler, R. *Can. J. Chem.* **1987**, *65*, 251–255.
9. Mąkosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1990**, *55*, 4979–4981.
10. The reaction of 2-fluoropyridine with aqueous hydrochloric acid to afford 2-pyridone has been reported: Bradlow, H. L.; Vander Werf, C. A. *J. Org. Chem.* **1949**, *14*, 509–515.
11. 2-Fluoropyridine has been converted to 3-methoxypyridine with sodium methoxide and 18-crown-6 with microwave irradiation: Lloung, M.; Loupy, A.; Marque, S.; Petit, Alain. *Heterocycles* **2004**, *63*, 297–308.
12. 2-Chloropyrimidine was converted in two steps to 2-pyrimidone via the 2-ethoxy ether: Al-Awadi, N.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1255–1258.
13. See Ref. 1, p 445.