JOC*Note*

Microwave-Assisted Trans-Halogenation Reactions of Various Chloro-, Bromo-, Trifluoromethanesulfonyloxy- and Nonafluorobutanesulfonyloxy-Substituted Quinolines, Isoquinolines, and Pyridines Leading to the Corresponding Iodinated Heterocycles†

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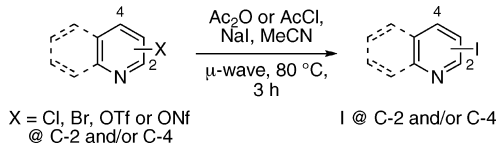

Microwave irradiation of certain chloro-, bromo-, trifluoromethanesulfonyloxy- and nonafluorobutanesulfonyloxy-substituted quinolines in the presence of acetic anhydride and sodium iodide leads, via a trans-halogenation process, to the corresponding iodides in high yield. Related conversions involving pyridines and isoquinolines can also be achieved under similar conditions.

The ready participation of aryl iodides in metalation processes and metal-catalyzed cross-coupling reactions has made them particularly valuable building blocks in medicinal chemistry, in materials science, and in total synthesis.[1] However, such compounds are often difficult to obtain, especially if the halogen is attached to a nitrogen-containing heteroaromatic framework.[2] Trans-halogenation protocols (sometimes characterized as aromatic Finkelstein reactions) involving a bromo- or chloro-precursor to the target iodide have been introduced in an effort to overcome such difficulties although many limitations still apply.[3] In 1947 Bruce demonstrated that a 2,4-di-iodinated pyridine could be prepared in quantitative yield by heating its dichloro-analogue with hydroiodic acid.[4] Variations on this sort of approach have been introduced over the intervening years wherein the ring nitrogen in pyridines has been activated through protonation,[5] silylation,[6] or acylation[7] and thereby facilitating a nucleophilic addition/elimination reaction (S_NAr reaction) involving iodide ion that leads to the target aryl halide.[8] The proton activation approach has been applied to quinolines[7,9] although Newkome[10] has shown that such conditions can lead to reductive dehalogenation when very electron-deficient pyridines are involved. Nickel- and copper-promoted trans-halogenation processes have been introduced over the last two decades[11] while, in 2002, Buchwald reported[12] a copper-catalyzed method for the conversion of aryl bromides into the corresponding iodides. Various relevant extensions of Buchwald's chemistry have since been introduced by his group.[13] Despite the useful advances involved, high reaction temperatures (i.e. >100 °C), extended reactions times (≥24 h), and/or strongly acidic conditions are often required and thus precluding the application of such techniques to substrates containing sensitive functionalities.

In connection with work directed toward the total synthesis of the alkaloid quinine, we recently reported a short and efficient synthesis of 4-iodo-6-methoxyquinoline.[14] The final step in the reaction sequence was the trans-halogenation of the corresponding bromide. The best conditions we could establish for effecting this conversion involved treating a solution of the substrate bromide in acetonitrile with sodium iodide and acetic anhydride and then subjecting the resulting mixture to microwave irradiation for 3 h at 80 °C. In this manner the desired iodo-compound was obtained in 94% yield. Since these sorts of conditions are much milder and involve shorter reaction times than those employed in many of the above-mentioned trans-halogenation protocols, we sought to investigate the scope of this method

† Strictly speaking, of course, the conversions of the title trifluoromethanesulfonyloxy- and nonafluorobutanesulfonyloxy-substituted systems into the corresponding iodides do not represent trans-halogenation processes, but since such substrates incorporate pseudohalogens it seems legitimate to apply this term to these cases as well as those true trans-halogenation processes detailed herein.

(1) See, for example: (a) Ila, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583, and references cited therein. (b) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555, and references cited therein.

(2) See, for example: (a) Merkushev, E. B. *Synthesis* **1988**, 923. (b) Barluenga, J.; González, J. M.; García-Martín, M. A.; Campos, P. J.; Asensio, G. *J. Org. Chem.* **1993**, *58*, 2058. (c) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487.

(3) Smalley, R. K. In *Quinolines*; Jones, G., Ed.; The Chemistry of Heterocyclic Compounds, Vol. 32, Part 1; John Wiley & Sons: London, UK, 1977; pp 418−426 and 679.

(4) Bruce, W. F.; Perez-Medina, L. A. *J. Am. Chem. Soc.* **1947**, *69*, 2571.

(5) See, for example: (a) Camparini, A.; Ponticelli, F.; Tedeschi, P. *J. Heterocycl. Chem.* **1977**, *14*, 435. (b) Newkome, G. R.; Roper, J. M. *J. Organomet. Chem.* **1980**, *186*, 147. (c) Seton, A. W.; Stevens, M. F. G.; Westwell, A. D. *J. Chem. Res. (S)* **2001**, 546. (d) Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett.* **2004**, *6*, 2917.

(6) Schlosser, M.; Cottet, F. *Eur. J. Org. Chem.* **2002**, 4181.

(7) See, for example: (a) Corcoran, R. C.; Bang, S. H. *Tetrahedron Lett.* **1990**, *31*, 6757. (b) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861. (c) Lennox, J. R.; Turner, S. C.; Rapoport, H. *J. Org. Chem.* **2001**, *66*, 7078.

(8) In certain instances no activation is required: Klingsberg, E. *J. Am. Chem. Soc.* **1950**, *72*, 1031.

(9) Wolf, C.; Tumambac, G. E.; Villalobos, C. N. *Synlett* **2003**, 1801.

(10) Newkome, G. R.; Moorfield, C. N.; Sabbaghian, B. *J. Org. Chem.* **1986**, *51*, 953.

(11) (a) Yang, S. H.; Li, C. S.; Cheng, C. H. *J. Org. Chem.* **1987**, *52*, 691 (nickel powder-promoted reaction). (b) Clark, J. H.; Jones, C. W. *Chem. Commun.* **1987**, 1409 (alumina or charcoal supported CuI-promoted reaction). (c) Lovell, J. M.; Joule, J. A. *Synth. Commun.* **1997**, *27*, 1209 (copper−bronze-promoted reaction). (d) Kosaka, Y.; Yamamoto, H. M.; Nakao, A.; Tamura, M.; Kato, R. *J. Am. Chem. Soc.* **2007**, *129*, 3054 (CuI-promoted reaction).

(12) (a) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844. For an extension of this chemistry to the synthesis of an iodinated quinoline see: (b) Uchiyama, M.; Furuyama, T.; Kobayashi, M.; Matsumoto, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 8404.

(13) (a) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890. (b) McNeill, E.; Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3785.

(14) Bissember, A. C.; Banwell, M. G. *Org. Prep. Proced. Int.* **2008**, *40*, 557.

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for preparing a range of iodinated nitrogen-containing heterocyclic systems. The outcomes of such studies are reported here.

The successful trans-halogenation reactions are presented in Table 1 and involved treating acetonitrile solutions of quinolines **1**, **3**, **5**, **7**, **8**, **10**, **12**, **13**, **15**, **16**, and **17**, the isoquinolines **19** and **21**, as well as the pyridines **22**, **24**, **25**, and **27** with sodium iodide and either acetic anhydride or acetyl chloride then subjecting the resulting mixture to microwave irradiation at 80 °C for the specified period. The substrates used for these studies were either commercially available or readily prepared by applying standard procedures to commercially available precursors. The yields of the substrates prepared by such means were not optimized.

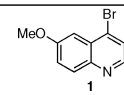
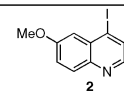
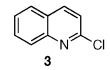
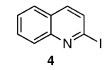
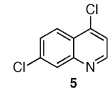
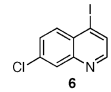
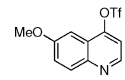
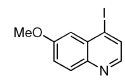
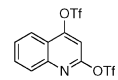
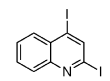
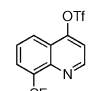
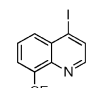
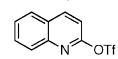
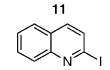
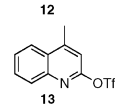
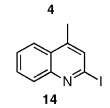
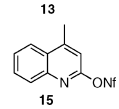
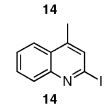
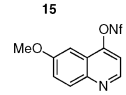
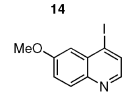
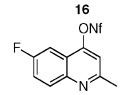
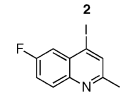
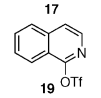
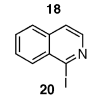
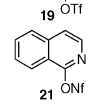
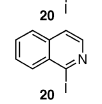
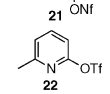
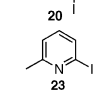
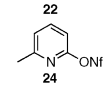
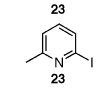
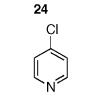
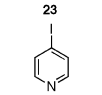
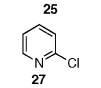
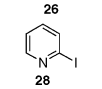
The results presented in Table 1 reveal that quinolines carrying a leaving group at C-2 and/or C-4 readily engage in the desired trans-halogenation reaction(s) and thereby afford the corresponding iodides in generally excellent yield. Significantly, compounds **5**, **7**, **10**, **16**, and **17** carrying potential leaving groups at C-6, C-7, or C-8 do not undergo iodination at these positions while additional results presented below also reveal (in keeping with expectations) a lack of reaction at C-3 and C-5 when these sites bear halogen substituents. In some instances it was found that using acetic anhydride as the activating agent (procedure A) provided better yields of product than when acetyl chloride was used for the same purpose (procedure B). This situation is attributed to coproduction of the corresponding aryl chloride when the latter activating agent was employed. Nevertheless, there were other cases where the latter procedure proved superior.

As expected, isoquinolines **19** and **21** carrying a potential leaving group at C-1 engage in the trans-halogenation reaction to give iodide **20** in excellent yield. Studies outlined below have established that C-1 is likely to be the only position on the isoquinoline framework where such a process can take place. Pyridines bearing a leaving group at C-2 or C-4 also participate in trans-halogenation reactions under the specified conditions, thus affording the anticipated iodinated products in generally good yield. The origins of the rather poor yield (33%) associated with the conversion of triflate **22** into iodide **23** remain unclear but can, seemingly, be addressed by using the corresponding nonaflate (**24**) as substrate. A further interesting observation is that when 1-chloroisoquinoline, rather than isoquinolin-1-yl trifluoromethanesulfonate (**19**), was used as the substrate for the trans-halogenation reaction then the yield of the corresponding iodide was only 45% and this was accompanied by significant quantities of a byproduct tentatively identified as an unsymmetrical 1,*X*′-biisoquinoline.

The success of these reactions is clearly dependent upon the acylation of the ring-nitrogen and the resulting activation of the halogenated (or pseudohalogenated) carbon toward a S_NAr reaction involving iodide as nucleophile. To ensure complete reaction, a 3-fold excess of sodium iodide was employed under those conditions involving acetic anhydride (procedure A) as the activating agent. When acetyl chloride was used for the same purpose (procedure B) then a 10-fold excess of sodium iodide was used so as to ensure a much higher iodide than chloride ion concentration in the reaction mixture. It is noteworthy that in all instances where an isoquinoline or pyridine was a substrate then the more vigorous conditions defined by procedure B were required to achieve good conversions into the target iodide.

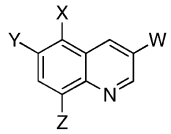
In keeping with expectations, substrates **29**−**35** all failed to engage in trans-halogenation reactions when subjected to the conditions defined by procedure A or B. The lack of reaction of substrate **36** at C-2 is a little surprising given the successful trans-halogenation of 2-chloropyridine (see entry 17 of Table 1) but clearly attributable to the presence of the C-3 chlorine.

TABLE 1. Outcomes of the Trans-Halogenation Reactions of Certain Substituted Quinolines, Isoquinolines, and Pyridines

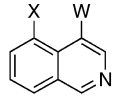
entry	substrate[a]	product	procedure[b]	yield[c] (%)
1	 **1**	 **2**	A	94
2	 **3**	 **4**	A	85
3	 **5**	 **6**	A	93
4	 **7**	 **2**	A	93
5	 **8**	 **9**	B	97
6	 **10**	 **11**	A	97
7	 **12**	 **4**	B	91
8	 **13**	 **14**	B	94
9	 **15**	 **14**	B	92
10	 **16**	 **2**	A	92
11	 **17**	 **18**	A	95
12	 **19**	 **20**	B	90
13	 **21**	 **20**	B	93
14	 **22**	 **23**	B	33
15	 **24**	 **23**	B	74
16	 **25**	 **26**	B	91
17	 **27**	 **28**	B	98

[a] The substrates used were either commercially available materials or readily prepared by conventional methods (see the SI). [b] Details of procedures A and B are provided in the SI. [c] All yields cited are of isolated and chromatographically purified materials.

It seems possible that the two chlorines attached to the pyridine ring in compound **36** inhibit the initial *N*-acylation process, thus precluding trans-halogenation under the conditions we report here. Of course, steric effects exerted by the two chlorines may also contribute to the lack of reactivity of compound **36**.



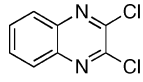
29 W = Br, X = Y = Z = H
30 X = Cl, W = Y = Z = H
31 Y = Br, W = X = Z = H
32 Z = Br, W = X = Y = H



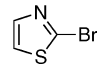
33 W = Br, X = H
34 X = Br, W = H

35 X = Br, W = H
36 W = X = Cl

We have undertaken a brief investigation of the capacity of other aromatic nitrogen heterocycles to participate in the title process but no useful outcomes have been observed. Thus, for example, attempts to effect trans-halogenation of the commercially available compounds **37** and **38** under either of the specified conditions have failed and only the starting compounds were recovered.



37



38

A final aspect of the present investigation was concerned with establishing if nucleophiles other than iodide could be induced to participate in S_NAr reactions under the conditions developed. However, upon exposing compound **6** to either acetic anhydride or acetyl chloride in the presence of various sources of fluoride, chloride, cyanide, and nitrite anions no evidence for the formation of the hoped-for substitution products could be obtained.

The protocols defined here provide a useful means for effecting the rather rapid trans-halogenation of various chlorinated, brominated, or pseudohalogenated quinolines, isoquinolines, and pyridines under mild conditions. The reaction pathways involved mean that the regioselectivities of these processes are entirely predictable. As such they should find use in the preparation of a range of iodinated aromatic nitrogen heterocycles.

Experimental Section

Trans-Halogenation Studies: Procedure A. Acetic anhydride (300 μL, 3.15 mmol) was added to a magnetically stirred suspension of the appropriate quinoline (1.26 mmol) and sodium iodide (565 mg, 3.78 mmol) in acetonitrile (2 mL) maintained at 18 °C. The ensuing reaction mixture was heated, for 3 h, at 80 °C in a microwave reactor then cooled and treated with potassium carbonate (1.5 mL of a 10% aqueous solution), sodium sulfite (1.5 mL of a 5% w/v aqueous solution), sodium thiosulfate (1.5 mL of a saturated aqueous solution), and dichloromethane (10 mL). The phases were separated, the aqueous layer was extracted with dichloromethane (3 × 5 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography.[15]

Trans-Halogenation Studies: Procedure B. Acetyl chloride (134 μL, 1.89 mmol) was added to a magnetically stirred suspension of the appropriate pyridine, quinoline, or isoquinoline (1.26 mmol) and sodium iodide (1.88 g, 12.6 mmol) in acetonitrile (2 mL) maintained at 18 °C. The ensuing reaction mixture was heated, for 3 h, at 80 °C in a microwave reactor then cooled and treated with potassium carbonate (3 mL of a 10% w/v aqueous solution), sodium sulfite (3 mL of a 5% w/v aqueous solution), sodium thiosulfate (3 mL of a saturated aqueous solution), and dichloromethane (20 mL). The phases were separated, the aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography.[15]

4-Iodo-6-methoxyquinoline (2)—From Substrate 1 via Procedure A. The previously reported iodide **2**[14] was prepared in 94% yield from starting material **2** according to procedure A as specified above and isolated by, flash chromatography, as a colorless, crystalline solid, mp 126 °C (lit.[14] mp 126 °C) (R_f 0.2 in 4:1 v/v hexane/ethyl acetate). ^{1}H NMR (300 MHz) δ 8.29 (br s, 1H), 7.99−7.89 (complex m, 2H), 7.65 (dd, J = 9.0 and 2.7 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (75 MHz) δ 158.9, 146.9, 143.7, 132.4, 131.4, 131.3, 122.9, 110.2, 109.2, 55.4; IR ν_{max} 3344, 2953, 1617, 1555, 1498, 1452, 1423, 1350, 1264, 1232, 1159, 1028 cm^{-1}; EI-MS m/z 285 ($M^{+\bullet}$,100%); HRMS m/z $M^{+\bullet}$ calcd for $C_{10}H_8{}^{127}INO$ 284.9651, found 284.9651. Anal. Calcd for $C_{10}H_8INO$: C, 42.13; H, 2.83; I, 44.51; N, 4.91. Found: C, 42.45; H, 3.19; I, 44.22; N, 4.96.

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Supporting Information Available: Detailed procedures and full characterization data for all compounds and ^{1}H and ^{13}C NMR spectra for compounds **8**, **9**, **10**, **11**, **16**, **17**, **18**, **21**, and **24** (new compounds). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.