Tetrahedron Letters,Vol.26,No.17,pp 2043-2046,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

IODINATION OF PHENOLS USING CHLORAMINE T AND SODIUM IODIDE

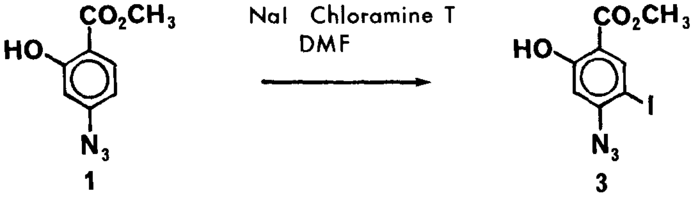
Tadashi Kometani, David S. Watt,* and Tae Ji*

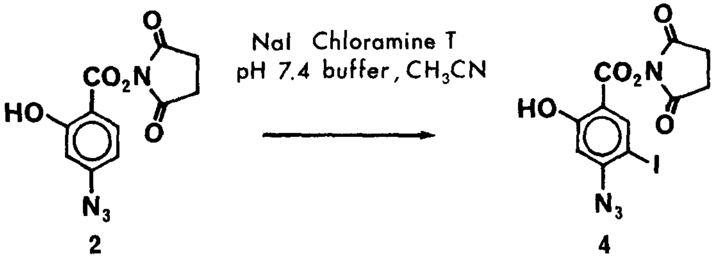
Departments of Chemistry and Biochemistry, University of Wyoming,
Laramie, WY 82071

Abstract. A convenient procedure for the iodination of many substituted phenols uses chloramine T and sodium iodide in DMF, DMSO, or acetonitrile.

In connection with the preparation of various cleavable, bifunctional cross-linking reagents[1] bearing a radioiodinated aryl azide moiety, we required a procedure for the direct iodination[2] of the aryl azide nucleus in the presence of other acid- or base-sensitive functional groups. Although there are a number of procedures[2] for the synthesis of aryl iodides, these methods are invariably incompatible with our particular needs. In the course of defining neutral conditions for this radioiodination, we have explored the scope of a sodium iodide/chloramine T iodination procedure[3] for various substituted phenols including those bearing azide functionality.

We have found that sodium iodide (1.2 equivalents) and chloramine T (1.2 equivalents) in DMF, DMSO or acetonitrile effected the iodination of various phenols including some of those previously reported to give only intractable products.[4] As shown in Table I, these conditions provided principally the monoiodinated material,[5] but if desired, increased equivalents of chloramine T and sodium iodide furnished the diodinated product.[5] The process accommodated both electron-withdrawing and electron-donating substituents but failed for those phenols bearing a *para*-oriented methoxy, amino, or acetamido group. Various aromatic compounds such as anisoles were also unreactive under these iodination conditions. Of particular interest to us were the findings that this iodination protocol proceeded in the presence (or absence) of a pH=7.4 buffer and succeeded in the presence of sensitive functionality such as an azide group in phenol 1 or an N-hydroxysuccimidyl ester in phenol 2.





The following is a typical experimental procedure. To a solution of 100 mg (0.657 mmol) of vanillin and 118 mg (0.789 mmol) of sodium iodide in 3 mL of DMF at 25°C was added 222 mg (0.789 mmol) of chloramine T (Aldrich). The mixture was stirred for 1 h. The product was diluted with water, acidified with 5% hydrochloric acid solution and extracted with ethyl acetate. The organic solution was washed successively with 5% sodium thiosulfate solution and brine and was dried over anhydrous magnesium sulfate. The crude product was crystallized from ethyl acetate to afford 172 mg (94%) of 5-iodovanillin: mp 179-180°C (lit mp 180°C); ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 3, OCH_3), 6.69 (s, 1, OH), 7.38 (d, 1, J = 1.6 Hz, C-2 H), 7.82 (d, 1, J = 1.6 Hz, C-6 H), 9.77 (s, 1, CHO).

Table I. Iodinations of Selected Phenols Using Chloramine T (1.2 eq) and Sodium Iodide (1.2 eq) in DMF (initial phenol concentration = 0.33M)

	Substrate	Conditions	Products (% Isolated Yield)
a	phenol	25°, 1 h	4-iodophenol[c] (97%)
b	2-cresol	25°, 1 h	4-iodo-2-cresol[d] (76%), 4,6-diiodo-2-cresol[e] (12%)
c	4-cresol	25°, 10 min	2-iodo-4-cresol[f] (60%), 2,6-diiodo-4-cresol[e] (21%)
		25°, 10 min[a]	2-iodo-4-cresol[f] (64%), 2,6-diiodo-4-cresol[e] (23%)
		25°, 10 min[a,b]	2,6-diiodo-4-cresol[e] (71%)
d	4-chlorophenol	25°, 1 h	4-chloro-2-iodophenol[g] (75%), 4-chloro-2,6-diiodophenol[g] (23%)

e	4-nitrophenol	25°, 1 h	2-iodo-4-nitrophenol[h] (69%)
f	4-tert-butylphenol	25°, 1 h	4-tert-butyl-2-iodophenol[i] (69%), 4-tert-butyl-2,6-diiodophenol[j] (25%)
g	methyl salicylate	25°, 1 h	methyl 5-iodosalicylate[k] (78%)
h	2-naphthol	25°, 1 h	1-iodo-2-naphthol[e] (66%)
i	2,6-dimethylphenol	25°, 1 h	2,6-dimethyl-4-iodophenol[l] (64%)
j	vanillin	25°, 1 h	5-iodovanillin[m] (94%)
k	17β-estradiol	25°, 20 min[a]	2-iodo-17β-estradiol[n] (27%), 4-iodo-17β-estradiol[n] (20%), 2,4-diiodo-17β-estradiol[o] (15%)
ℓ	**1**	25°, 1 h	**3** (88%)
m	**2**	25°, 1 h[a]	**4** (42%)[p]

---

a, using 1:6 pH 7.4 buffer:DMF; b, using 2.2 equivalents each of chloramine T and NaI; c, F. B. Dains and F. Eberly, Org. Syn. Coll. Vol. 2, 355 (1943); d, G. M. Robinson, J. Chem. Soc., 1078 (1916); e, K. T. Potts, ibid., 3711 (1953); f, O. Dimroth, Chem. Ber., **35**, 2853 (1902); g, P. S. Varma and K. M. Yashoda, J. Indian Chem. Soc., **16**, 477 (1939); h, H. H. Hodgson and F. H. Moore, J. Chem. Soc., 2260 (1925); i, G. E. Stokkev, A. A. Deana, S. J. de Solms, E. M. Schultz, R. L. Smith, E. J. Cragoe, Jr., J. E. Baer, C. T. Ludden, H. F. Russo, A. Scriabine, C. S. Sweet, and L. S. Watson, J. Med. Chem., **23**, 1414 (1980); j, P. G. Sennikov, V. A. Kuznetsov, A. N. Egorochkin, S. E. Skobelena, I. G. Kosolapova, Ya. I. Korenman, and D. V. Muslin, Zh. Obshch. Khim., **51**, 1182 (1981); k, M. Covallo, Chim. Ther., **2**, 73 (1967); l, K. Heicken, Angew Chem., **52**, 263 (1939); m, R. M. Hann, J. Am. Chem. Soc., **47**, 1998 (1925); n, F. Sweet, T. B. Patrick, and J. M. Mudd, J. Org. Chem., **44**, 2296 (1979); o, S. Albert, R. D. H. Heard, C. P. Leblond, and J. Saffran, J. Biol. Chem., 157, 247 (1949); p, **4** was isolated by crystallization but yield was determined by conversion of **4** to an N-(n-butyl)amide derivative.

Acknowledgement. We thank the National Institutes of Health (HD-17639, HD-18702) for their generous financial support.

References

1. (a) H. Bayley, "Laboratory Techniques in Biochemistry and Molecular Biology", T. S. Work and R. H. Burdon, eds., Elsevier, Amsterdam, 1983; (b) V. Chowdhry and F. H. Westheimer, Annu. Rev. Biochem., **48**, 293 (1979).

2. A. Roedig, "Methoden der Organischen Chemie (Houben-Weyl)", Georg Thieme Verlag, Stuttgart, 1960, p. 517f.

3. For the use of chloramine T for the chlorination of phenols, see (a) T. Higuchi and A. Hussain, *J. Chem. Soc. B*, 549 (1967); (b) M. Sanchez Vera, G. N. Bianco de Salas, and A. E. A. Mitta, *Argent., Com. Nac. Energ. At., [Inf.]*, 342 (1973) [*Chem. Abst.*, **82**, 72596q (1975)]; (c) J. M. Antelo, J. M. Cachaza, J. Casado, and M. A. Herraez, *An. Quim.*, **70**, 461 and 555 (1974); (d) V. Balasubramanian and V. Thiagarajan, *Int. J. Chem. Kinet.*, **7**, 605 (1975); (e) R. Lange, J. Schliemann, R. Friebe, and F. Linow, *Nahrung*, **24**, 447 (1980); (f) K. Rengarajan, K. Vaidyanathan, V. S. Srinivasan, and N. Venkatasubramanian, *Indian J. Chem., Sect. A*, **19A**, 79 (1980).

4. Sodium iodide and chloramine T *in acetic acid* was reported previously to effect the iodination of certain phenols: B. Jones and E. N. Richardson, *J. Chem. Soc.*, 713 (1953), but under these conditions, a variety of phenols gave intractable products which under the conditions developed by us, gave useful, iodinated products.

5. All new compounds possessed infrared, ^{1}H NMR, mass spectra, and satisfactory combustion analysis data in accord with assigned structures.

(Received in USA 29 January 1985)