

## Acid-Mediated Reaction of Bis(pyridine)iodonium(I) Tetrafluoroborate with Aromatic Compounds. A Selective and General Iodination Method

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Reaction of aromatic compounds with bis(pyridine)iodonium(I) tetrafluoroborate (IPy<sub>2</sub>BF<sub>4</sub>) in the presence of HBF<sub>4</sub> or CF<sub>3</sub>SO<sub>3</sub>H in CH<sub>2</sub>Cl<sub>2</sub> at room temperature furnishes monoiodo derivatives with excellent regioselectivity and yields. Use of either acid gives comparable results with activated aromatics, whereas CF<sub>3</sub>SO<sub>3</sub>H is much more effective in the iodination of deactivated aromatics.

Metal-mediated transformations of carbon-iodine bonds in aromatic compounds can provide access to difficult patterns of aromatic substitution.<sup>1</sup> Radioactively labeled iodoaromatic compounds<sup>2</sup> are used in radioimmunoassay studies and in nuclear magnetic imaging.<sup>3</sup> The lack of general methods for preparing iodinated aromatic compounds has constrained more widespread use of them.<sup>4</sup> Alternative reagents and procedures have been developed to overcome this limitation.<sup>5,6</sup>

The reaction of bis(pyridine)iodonium(I) tetrafluoroborate (IPy<sub>2</sub>BF<sub>4</sub>) with unsaturated compounds in the presence of HBF<sub>4</sub> has been reported.<sup>7</sup> In a recent communication we described the preparation of iodinated aromatic compounds with that reagent.<sup>8</sup> We now report the synthesis of iodinated aromatic compounds directly from aromatic substrates with IPy<sub>2</sub>BF<sub>4</sub>.

### Results and Discussion

Treating a mixture of IPy<sub>2</sub>BF<sub>4</sub> and an aromatic compound with an acid in dichloromethane at room temperature gave monoiodinated products in good yields. Initially, reactions were carried out using HBF<sub>4</sub> as the acid to neutralize pyridine<sup>9</sup> and liberate the iodinating agent (Table I). The stoichiometry of the reaction was studied using benzene as a model compound. An acceptable yield of iodobenzene was obtained with a 1:2 molar ratio of IPy<sub>2</sub>BF<sub>4</sub>/HBF<sub>4</sub>. The yield was improved by using a slight excess of IPy<sub>2</sub>BF<sub>4</sub> (1.1 equiv) with respect to the arene. The order of addition of the reagents also influences the yield. Adding IPy<sub>2</sub>BF<sub>4</sub> gradually to a CH<sub>2</sub>Cl<sub>2</sub> solution of acid and benzene gives a higher yield. By this procedure, benzene can be iodinated at room temperature in 15 min (Table I, entry 1). Naphthalene and haloarenes are best iodinated following the same protocol. On the other hand, iodination of arenes containing electron-donating groups is better accomplished by adding HBF<sub>4</sub> dropwise to a solution containing the arene and IPy<sub>2</sub>BF<sub>4</sub>.

The HBF<sub>4</sub>-mediated iodination of bromobenzene with IPy<sub>2</sub>BF<sub>4</sub> gave only 30% yield of 4-iodobromobenzene (Table I, entry 11). Increasing the reaction time to 10 h did not improve the yield, and it decreased when the reaction mixture was heated at 83 °C in dry 1,2-dichloroethane. On the other hand, use of triflic<sup>10</sup> acid instead of HBF<sub>4</sub> improved the yield of 4-iodobromobenzene, particularly when the reaction time was increased to 2 h (Table I, entries 12-14). The combination triflic acid-IPy<sub>2</sub>BF<sub>4</sub> turned out to be a more powerful iodinating agent than HBF<sub>4</sub>-IPy<sub>2</sub>BF<sub>4</sub>. It iodinated nitrobenzene and methyl benzoate, which were not affected by HBF<sub>4</sub>-IPy<sub>2</sub>BF<sub>4</sub> (Table I, entries 27, 29, 30, and 33).

Minor differences between the two acids were found for the iodination of benzene and alkylbenzenes. Under the conditions previously mentioned for iodinating benzene, triflic acid gave better results, especially when the reaction time was extended to 2 h (Table I, entries 2 and 3). For *tert*-butylbenzene as the starting aromatic, the steric

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(1) For chemoselective transformations of a C-I bond in the presence of a C-Br bond through a Heck reaction, see: Plevyak, J. E.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* 1979, 44, 4078. Unrau, C. M.; Campbell, M. G.; Snieckus, V. *Tetrahedron Lett.* 1992, 33, 2773. For a review on the Heck reaction, see: Heck, R. F. *Org. React.* 1982, 27, 345.

(2) The isotopes of iodine have advantages over other extensively used radiolabels such as <sup>14</sup>C or <sup>3</sup>H in the type of radiation they emit on decay (for iodine  $\gamma$ -emitters) and the relative shortness of their half-lives.

(3) For a review on the preparation of radioiodinated small molecules and references to their uses, see: Seevers, R. H.; Counsell, R. E. *Chem. Rev.* 1982, 82, 575.

(4) Aromatic electrophilic iodination is not generally recognized as the simplest and most conventional procedure for synthesizing iodinated derivatives. See, for instance, Warren, S. *Organic Synthesis*; Wiley: New York, 1986; pp 10-12.

(5) For a review covering the literature reported mainly from 1965 to 1985, see: Merkusev, E. B. *Russ. Chem. Rev. (Engl. Transl.)* 1984, 53, 343. Merkushev, E. B. *Synthesis* 1988, 923. For a review up to 1960, see: Roedig, A. *Houben-Weyl*; Georg Thieme Verlag: Stuttgart, 1960, Vol. V/4, p 517.

(6) For recent references, see: (a) Wilson, S. R.; Jacob, L. A. *J. Org. Chem.* 1986, 51, 4833. (b) Boothe, R.; Dial, C.; Conaway, R.; Pagni, R. M.; Kabalka, G. W. *Tetrahedron Lett.* 1986, 27, 2207. (c) Moerlein, S. M. *J. Org. Chem.* 1987, 52, 664. (d) Radner, F. *J. Org. Chem.* 1988, 53, 3548. (e) Sy, W. W.; Lodge, B. A. *Tetrahedron Lett.* 1989, 30, 3769. (f) Rozen, S.; Zamir, D. *J. Org. Chem.* 1990, 55, 3552. (g) Edgar, K. J.; Falling, S. N. *J. Org. Chem.* 1990, 55, 5287. (h) Galli, C. *J. Org. Chem.* 1991, 56, 3238. (i) Christiansen, J. V.; Feldthus, A.; Carlsen, L. *J. Chem. Res., Synop.* 1991, 300. (j) Yue, E. W.; Gerdes, J. M.; Mathis, C. A. *J. Org. Chem.* 1991, 56, 5451. (k) Bovonsombat, P.; Angara, G. J. *McNelis, E. Syntlett* 1992, 131.

(7) Barluenga, J.; Campos, P. J.; González, J. M.; Suárez, J. L.; Asensio, G. *J. Org. Chem.* 1991, 56, 2234.

(8) Barluenga, J.; González, J. M.; García-Martín, M. A.; Campos, P. J.; Asensio, G. *J. Chem. Soc., Chem. Commun.* 1992, 1016.

(9) We used tetrafluoroboric acid as a 54% ethereal solution commercially available from E. Merck (Germany). For a comment on the neutralization of pyridine in these reactions, see ref 7 in this paper.

(10) (a) For a review on triflic acid, see: Stang, P. J.; White, M. R. *Aldrichim. Acta* 1983, 16, 15. (b) For iodination of benzene in triflic acid as solvent, see: Shimizu, A.; Yamataka, K.; Isoya, T. *Bull. Chem. Soc. Jpn.* 1985, 58, 1611.

Table I. Room-Temperature Iodination of Aromatic Compounds by Acid Treatment of IPy<sub>2</sub>BF<sub>4</sub> (See Chart I)

entry	starting material	acid	time (h)	ArI (yield %) <sup>a</sup>
1	benzene	HF <sub>4</sub>	0.25	1 (48)
2	benzene	CF <sub>3</sub> SO <sub>3</sub> H	0.25	1 (60)
3	benzene	CF <sub>3</sub> SO <sub>3</sub> H	2	1 (85)
4	<i>tert</i> -butylbenzene	HF <sub>4</sub>	0.10	2 (50)
5	<i>tert</i> -butylbenzene	CF <sub>3</sub> SO <sub>3</sub> H	0.25	2 (93)
6	<i>m</i> -xylene	HF <sub>4</sub>	0.25	3 (80) <sup>b</sup>
7	mesitylene	HF <sub>4</sub>	0.10	4 (99)
8	mesitylene	CF <sub>3</sub> SO <sub>3</sub> H	0.10	4 (99)
9	1,2,3-trimethylbenzene	HF <sub>4</sub>	0.10	5 (99) <sup>c</sup>
10	pentamethylbenzene	HF <sub>4</sub>	0.10	6 (99)
11	bromobenzene	HF <sub>4</sub>	0.25	7 (30) <sup>d</sup>
12	bromobenzene	CF <sub>3</sub> SO <sub>3</sub> H	0.10	7 (40) <sup>e</sup>
13	bromobenzene	CF <sub>3</sub> SO <sub>3</sub> H	0.50	7 (74) <sup>e</sup>
14	bromobenzene	CF <sub>3</sub> SO <sub>3</sub> H	2	7 (90) <sup>e</sup>
15	chlorobenzene	HF <sub>4</sub>	0.25	8 (28) <sup>f</sup>
16	chlorobenzene	CF <sub>3</sub> SO <sub>3</sub> H	0.50	8 (78) <sup>e</sup>
17	naphthalene	HF <sub>4</sub>	0.20	9 (55) <sup>e</sup>
18	naphthalene	CF <sub>3</sub> SO <sub>3</sub> H	0.20	9 (77) <sup>e</sup>
19	phenol	CF <sub>3</sub> SO <sub>3</sub> H	0.50	10 (93) <sup>g</sup>
20	anisole	HF <sub>4</sub>	0.10	11 (99)
21	anisole	CF <sub>3</sub> SO <sub>3</sub> H	0.10	11 (99)
22	4-bromoanisole	CF <sub>3</sub> SO <sub>3</sub> H	1	12 (98)
23	1,3,5-trimethoxybenzene	CF <sub>3</sub> SO <sub>3</sub> H <sup>h</sup>	0.25	13 (86)
24	aniline	HF <sub>4</sub>	0.10	14 (90)
25	<i>N,N</i> -dimethylaniline	HF <sub>4</sub>	0.10	15 (98)
26	indole	HF <sub>4</sub> <sup>i</sup>	0.25	16 (93)
27	nitrobenzene	HF <sub>4</sub>	16	21 (0)
28	2-nitroaniline	HF <sub>4</sub>	0.25	17 (83)
29	methylbenzoate	HF <sub>4</sub>	15	18 (0)
30	methylbenzoate	CF <sub>3</sub> SO <sub>3</sub> H	14	18 (84) <sup>j</sup>
31	benzoic acid	CF <sub>3</sub> SO <sub>3</sub> H	10	19 (86) <sup>j</sup>
32	benzaldehyde	CF <sub>3</sub> SO <sub>3</sub> H	10	20 (80) <sup>j</sup>
33	nitrobenzene	CF <sub>3</sub> SO <sub>3</sub> H	14	21 (82) <sup>j</sup>

<sup>a</sup> Yields are based on pure isolated compounds and referred to the starting aromatic compounds, unless otherwise noticed. <sup>b</sup> Yield based on a 6:1 mixture of 4-iodo-1,3-dimethylbenzene and 2-iodo-1,3-dimethylbenzene, respectively (by <sup>1</sup>H NMR). <sup>c</sup> Traces of 5-iodo-1,2,3-trimethylbenzene could be detected in the crude reaction mixture by <sup>1</sup>H NMR. <sup>d</sup> Containing 6% of the ortho-isomer by GC-EM. <sup>e</sup> Only traces of the ortho-isomer are observed. <sup>f</sup> Containing 7% of the ortho-isomer by GC-EM. <sup>g</sup> Reaction at -60 °C. <sup>h</sup> Catalytic amounts of acid (5%) employed. <sup>i</sup> Almost quantitative conversion is observed from the crude.

demand of the substituent led to the exclusive formation of the para-isomer with either acid (Table I, entries 4 and 5).<sup>11</sup> There were no significant differences between the two acids in the iodination of polyalkylbenzenes (Table I, entries 6–10). Although limitations for the iodination of polycyclic aromatic hydrocarbons have been described,<sup>12</sup> IPy<sub>2</sub>BF<sub>4</sub> iodinated naphthalene regioselectively with either acid to afford 1-iodonaphthalene (Table I, entries 17 and 18). The general trends in these reactions are similar to those of other electrophilic processes: enhancement of reactivity with increasing number of alkyl groups attached to the benzene nucleus, steric hindrance affecting ortho/para ratios, and relative reactivities.<sup>13</sup>

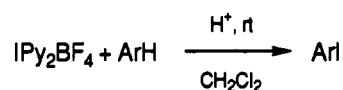
Aromatic compounds that bear electron-donating substituents are highly reactive toward the reagent. Attempts to iodinate phenol with IPy<sub>2</sub>BF<sub>4</sub> at room temperature led to the formation of complex mixtures, but at -60 °C a clean reaction took place with either acid, giving almost

(11) When toluene is the starting material, both methods behave alike, providing better yields of iodinated products than for benzene (for HF<sub>4</sub>, 75% combined yield, but now as a mixture of regioisomers ortho:para = 55:45 by <sup>1</sup>H NMR).

(12) Suzuki, H.; Kando, A.; Inouye, M.; Ogawa, T. *Synthesis* 1986, 121.

(13) (a) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* 1963, 1, 34. (b) Pross, A. *Adv. Phys. Org. Chem.* 1977, 14, 69.

Scheme I



H<sup>+</sup>: HBF<sub>4</sub> or CF<sub>3</sub>SO<sub>3</sub>H

quantitative conversion to iodophenol with only traces of 2-iodophenol (Table I, entry 19). Anisole gave a much cleaner reaction at room temperature. With either acid, rapid formation of only 4-iodoanisole was achieved. Analogous behavior was observed for 4-bromoanisole (entries 20–22). Even 1,3,5-trimethoxybenzene was iodinated by IPy<sub>2</sub>BF<sub>4</sub> at room temperature. However, when the usual amount of acid was added (twice the stoichiometric amount of IPy<sub>2</sub>BF<sub>4</sub>), significant (20%) formation of a diiodo compound was noted.<sup>14</sup> Use of only 0.10 equiv of triflic acid minimized the formation of byproducts and gave 4-iodo-1,3,5-trimethoxybenzene in 86% yield (entry 23).

Aniline and *N,N*-dimethylaniline were monoiodinated exclusively in the 4 position (entries 24, 25) without contamination by polyiodinated derivatives. Under the same conditions indole gave an intractable mixture.<sup>15</sup> Reducing the amount of HBF<sub>4</sub> to 0.10 equiv furnished 3-iodoindole in 93% yield.<sup>16</sup>

The triflic acid-IPy<sub>2</sub>BF<sub>4</sub> reagent was far superior to HBF<sub>4</sub>-IPy<sub>2</sub>BF<sub>4</sub> for iodination of benzenes carrying electron-withdrawing substituents (entries 27 and 29–33). In a representative experiment, the reagents were mixed under nitrogen in dichloromethane with vigorous magnetic stirring (aromatic compound:IPy<sub>2</sub>BF<sub>4</sub>:triflic acid = 1:1.1:2.2). A copious precipitate formed, and the mixture was allowed to stand at room temperature overnight. Conventional isolation and purification techniques afford pure meta-iodinated derivatives in excellent yields (entries 30–33). Inspection of the crude reaction mixtures by GC-EM and by <sup>1</sup>H and <sup>13</sup>C NMR did not reveal the presence of other regioisomers. Nitrobenzene reacted sluggishly under these conditions, but running the reaction with an excess of iodinating agent (nitrobenzene:IPy<sub>2</sub>BF<sub>4</sub>:triflic acid = 1:3:6) furnished, after purification, 82% of isolated 3-iodonitrobenzene (entry 33).<sup>17</sup>

Our results can be rationalized by an electrophilic aromatic substitution mechanism. The observed effects on the reactivity of individual aromatics, steric factors, and regioisomer distribution are compatible with those exhibited by other electrophilic substitutions on aromatic compounds.<sup>18</sup>

## Experimental Section

**General Methods.** The equipment and procedures used have been described.<sup>7</sup> IPy<sub>2</sub>BF<sub>4</sub> was prepared by a previously reported

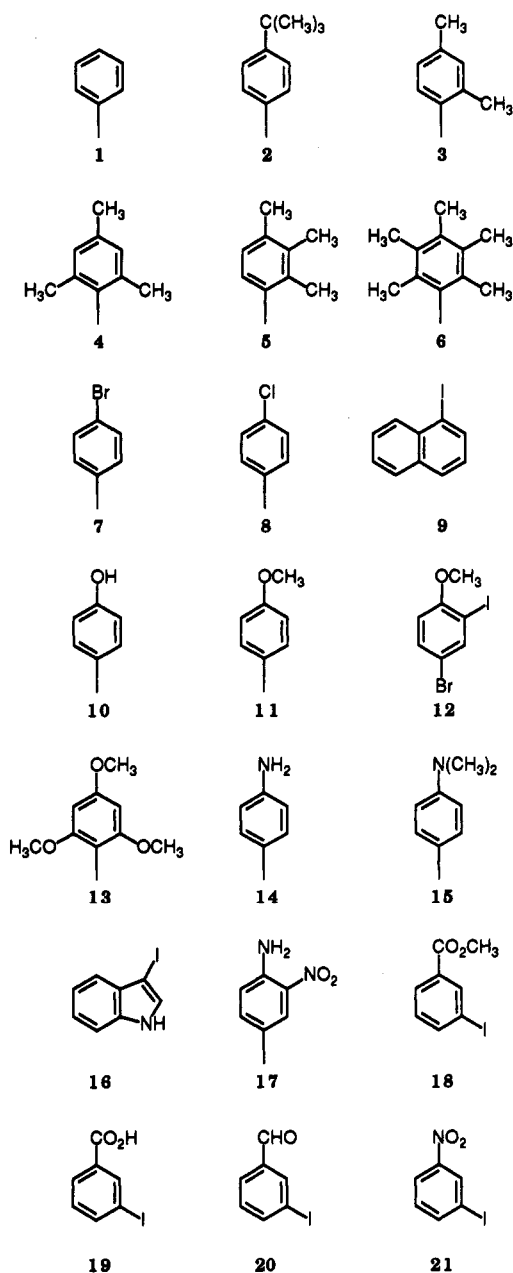
(14) For 2,4-diiodo-1,3,5-trimethoxybenzene: mp 130 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.17 (s, 1 H), 3.84 (s, 6 H), 3.78 (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 160.2 (doublet), 91.7, 72.4, 60.5, 56.7; MS *m/z* 372 (M<sup>+</sup>).

(15) For iodinations of indole, see: (a) Bocci, V.; Pala, G. *Synthesis* 1982, 1096. (b) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* 1982, 47, 757. (c) Bergman, J.; Venemalm, L. *J. Org. Chem.* 1992, 57, 2495.

(16) Careful workup of the reaction mixture, followed by gentle removal of pyridine under vacuum and short-path column filtration on alumina (hexane:ether = 6:1, as eluent), affords solid 3-iodoindole; mp 74 °C dec (recrystallized from a small amount of ethanol) (lit.<sup>15a</sup> mp 76 °C). The compound is very unstable (even protected from the light and stored under nitrogen), and it darkens in a short period of time.

(17) For previous iodinations of nitrobenzene, see: (a) Arotsky, J.; Butler, R.; Darby, A. C. *J. Chem. Soc. C* 1970, 1480. (b) Kobayashi, Y.; Kumadaki, I.; Yoshida, T. *J. Chem. Res. Synop.* 1977, 215. (c) Barluenga, J.; Campos, P. J.; González, J. M.; Asensio, G. *J. Chem. Soc., Perkin Trans. 1* 1984, 2623.

Chart I



procedure.<sup>19</sup> Aromatic compounds were commercial grade and used as purchased.

**Typical Iodination Method.** IPy<sub>2</sub>BF<sub>4</sub> (1.86 g, 5 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) in an oven-dried flask at rt under N<sub>2</sub>. The aromatic compound (4.5 mmol) was then added to the solution. A solution of the acid (10 mmol, 0.88 mL of CF<sub>3</sub>SO<sub>3</sub>H or 1.48 mL of a 54% ethereal solution of HBF<sub>4</sub>) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added over a period of 3 min to the magnetically stirred mixture. Reactions were monitored by TLC

and/or GC (for very reactive starting materials, simple inspection indicated instantaneous reaction by disappearance of the color in the mixture). Reaction times are specified in Table I. Reaction mixtures were then treated with aqueous sodium thiosulfate, extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine, and dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>). Solvents were removed at reduced pressure. The resulting mixtures were filtered through an alumina column (hexane:ether = 5:1), affording the iodinated derivatives. Further purification was achieved by crystallization (typically from ethanol or hexane), vacuum sublimation, or distillation at reduced pressure (compounds 1, 2, 3, 5, 9, and 18). Yields of iodinated aromatic compounds are summarized in Table I.

Exceptions to this general procedure are the following:

For HBF<sub>4</sub> reactions of benzene, naphthalene, chlorobenzene, and bromobenzene, the order of addition of reagents was modified as described in the text.

For iodination of nitrobenzene (entry 33 in Table I) the molar ratio of reagents was nitrobenzene:IPy<sub>2</sub>BF<sub>4</sub>:triflic acid = 1:3:6.

For iodination of 1,3,5-trimethoxybenzene and indole (entries 23 and 26 in Table I) the amount of acid used was 5% of the amount described in the general procedure.

The reaction of phenol (entry 19 in Table I) was run at -60 °C. The reaction was quenched by pouring the cold mixture into an excess of water.

**Characterization of Iodinated Products.** The compounds prepared have been previously described in the literature and were identical with commercial samples or had data in agreement with reported literature values.<sup>20,21</sup>

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**Supplementary Material Available:** <sup>13</sup>C NMR signal listings and selected *m/z* values from MS as representative data (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(18) For a general reference on widely accepted treatment of electrophilic aromatic substitution, see: (a) March, J. *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 4th ed.; Wiley: New York, 1992; pp 501-521. For a frontier orbital explanation of the observed para regioselectivity for strongly activated aromatic compounds, see: (b) Fleming, I. *Frontier Orbital and Organic Chemical Reactions*; Wiley: New York, 1978; pp 62-65. (c) Tedder, J. M.; Nechvatal, A. *Pictorial Orbital Theory*; Pitman: London, 1985; pp 93-100. For a charge-transfer formulation, see: (d) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* 1981, 103, 7240.

(19) Barluenga, J.; Rodríguez, M. A.; Campos, P. J. *J. Org. Chem.* 1990, 55, 3104.

(20) A list of Beilstein references (from the H series) is given below: 1(5,215); 2(5,416); 3(5,376); 4(5,409); 6(5,444); 7(5,223); 8(5,221); 9(5,550); 10(6,208); 11(6,208); 12(6,209); 13(EI,6,547); 14(12,670); 15(12,671); 16(20,310); 17(12,745); 18(9,365); 19(9,365); 20(7,240); 21(5,253).

(21) See also Keefer et al. (Keefer, R. M.; Andrews, L. J. *J. Am. Chem. Soc.* 1956, 78, 5623) for discrepancies with respect to the previously reported mp for compound 6. We found mp 135 °C, in good agreement with those authors. For reference to compound 5 see: Keefer, R. M.; Andrews, L. J. *J. Am. Chem. Soc.* 1955, 77, 4202.