Communications

Direct Aromatic Iodination Using IF Prepared from I_2 and F_2

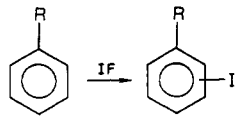
Summary: IF, made directly from the corresponding elements, may be used without any catalyst as an electrophilic iodinating agent in its reactions with activated and deactivated aromatic rings.

Sir: Of all aromatic halogenations, iodination suffers most from lack of versatility in methods of preparation. Direct iodination requires the presence of oxidizing agents such as HNO_3, which first oxidizes the iodine, while the more popular indirect method starts with an appropriate aniline derivative which is converted to the corresponding diazonium salt and quenched with iodine or KI.

As part of our goal to demonstrate that F_2 can serve as a unique reagent, even for the preparation of fluorine free products,[1] we report a method for the direct iodination of activated and deactivated aromatic rings.

A cold (−78 °C) suspension of iodine in $CFCl_3$ reacts with F_2 to produce yet another suspension proved to be IF.[2] This reagent seems to be less reactive then ClF or BrF, since it is apparently a cluster compound with molecules interconnected through I···F bridges.[3] Still, the difference in electronegativity of the atoms enables ionic reactions to occur with various organic substrates.[2a,b] This inherent polarity is the basis of our belief that this compound can serve as a source for electrophilic iodine strong enough to react with most types of aromatic compounds without the help of any external Friedel–Crafts catalyst.[4]

Toluene reacts with IF at −78 °C to produce a 1:1 mixture of *o*- and *p*-iodotoluene in a combined yield of 65%. Raising the temperature to −20 °C enables the introduction of an additional iodine atom and 2,4-diiodotoluene is formed in about 50% yield. Similar behavior was observed with benzene, where *p*-diiodobenzene could be obtained in greater than 70% yield. More weakly activated compounds like phenyl acetate are iodinated at the para position in 40% yield. When the aromatic ring is strongly activated, as in the case of anisole, only tars are produced, even at −78 °C. However, from 4-nitroanisole, 2-iodo-4-nitroanisole was isolated in 80% yield.[5]



Perhaps the most important feature of this reaction is the ability of this reagent to iodinate deactivated aromatic rings. Although nitrobenzene failed to react, benzonitrile produced *m*-iodobenzonitrile in good yield, but only in moderate conversion, even after 16 h. Ethyl benzoate and benzaldehyde however were fully converted to the corresponding *m*-iodo derivatives, each in 85% yield, although a relatively long reaction time, up to 16 h, was required for ethyl benzoate.

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Registry No. IF, 13873-84-2; PhMe, 108-88-3; *o*-IC_6H_4Me, 615-37-2; *p*-IC_6H_4Me, 624-31-7; 2,4-$(I)_2$-MeC_6H_3, 32704-08-8; PhH, 71-43-2; PhI, 591-50-4; *p*-IC_6H_4I, 624-38-4; PhOAc, 122-79-2; *p*-IC_6H_4OAc, 33527-94-5; *p*-$NO_2C_6H_4OMe$, 100-17-4; 1-OMe-2-I-4-$NO_2C_6H_3$, 5399-03-1; PhCN, 100-47-0; *m*-IC_6H_4CN, 69113-59-3; $PhCO_2Et$, 93-89-0; *m*-$IC_6H_4CO_2Et$, 58313-23-8; PhCHO, 100-52-7; *m*-IC_6H_4CHO, 696-41-3; PhOMe, 100-66-3; $PhNO_2$, 98-95-3.

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(2) (a) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342. (b) Rozen, S.; Brand, M. *J. Org. Chem.* **1986**, *51*, 222. (c) Schmeisser, M.; Sartori, P.; Naumann, D. *Chem. Ber.* **1970**, *103*, 880.

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(4) The same reasoning led us to explore first the possibility of using the much more reactive BrF for similar purposes. Rozen, S.; Brand, M. *J. Chem. Soc., Chem. Commun.* **1987**, 752.

(5) Experimental details for IF preparation at −78 °C can be found in ref 2a. A cold (−78 °C) $CHCl_3$ solution of the aromatic substrate was added to the IF suspension. The reaction was vigorously agitated with a Vibromixer (ref 2a) and monitored by GC. In the case of deactivated aromatic substrates the cooling bath was removed after 1 h and the reaction temperature was allowed to increase gradually to room temperature (about 2 h). Most of the aromatic iodination took place at that time although agitating for a longer period at room temperature increased the yields somewhat. The reaction mixture was then poured into a thiosulfate solution to cause complete reduction of excess I_2 and IF. The organic layer was washed with carbonate until neutral and the products were purified either by chromatography or crystallization. They were fully characterized and were shown to be identical with authentic samples or their spectral data were in excellent agreement with those reported in the literature.

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Chlorination, Bromination, and Oxygenation of the Pyridine Ring Using AcOF Made from F_2

Summary: Acetyl hypofluorite reacts with pyridines in halogenated solvents or alcohols to give the corresponding 2-halo- or 2-alkoxypyridines.

Sir: Regiospecific halogenation of a pyridine is a formidable task. The reactions are usually carried out at several hundred degrees and in many cases require reagents such as oleum. Since the nature of the halogenating agent is sensitive to changes in conditions it is difficult to define the precise nature of the reacting species, resulting usually in mixtures of several halogenated products in low to moderate yields. Regiospecific substitution of pyridinic hydrogen by an alkoxy group has not yet been achieved. Despite these limiting factors these reactions have been dominant in the recent pyridine related chemical literature.[1]

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We report here a new type of reaction[2] which accomplishes such substitutions rapidly, in good yields, and under very mild conditions. Developing a net positive charge on the carbon next to the nitrogen atom should facilitate selective ionic reactions. To achieve this goal, however, one should attack the basic nitrogen with a strong electrophile which will decrease the back donation of the nitrogen's lone pair electrons. In addition, after its job is completed this electrophile should leave the heterocyclic ring and restore the aromaticity. Naturally electrophilic fluorine would seem to be the best possible candidate for this purpose.

While under appropriate conditions both F_2 and several fluoroxy reagents can serve as a source for electrophilic fluorine,[3] acetyl hypofluorite (AcOF)[4] seems to be the best for the present purpose. It is the mildest fluoroxy agent[5] and yet is reactive enough to add to certain aromatic rings.[6] We have found lately that such 1,2 additions also take place on some heterocyclic systems, apparently through an initial attack of the electrophilic fluorine on the nitrogen atom.[7]

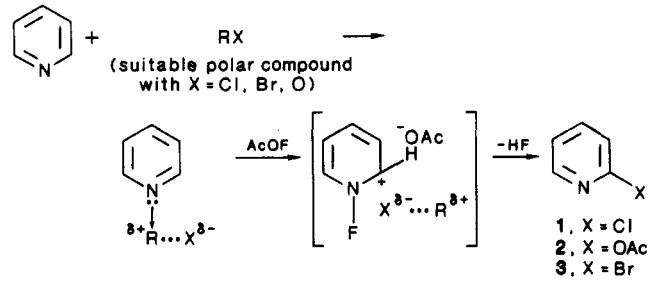
Since the addition of AcOF to double bonds is largely syn,[8] it has been questioned whether this reaction is a four-centered or a stepwise one. Addition of external nucleophiles such as Cl^- or Br^- did not affect the outcome of the reaction, possibly because of their limited solubility and the speed of the reaction between a double bond and AcOF. If, however, the external nucleophile were brought very close to the reactive center, and if indeed the reaction is a stepwise one, the nucleophilic specie would have a much better chance to compete successfully with the acetoxy anion.

When a solution of acetyl hypofluorite, prepared in $CFCl_3$ using F_2, was added at room temperature to pyridine dissolved in methylene chloride,[9] an instantaneous reaction took place. Two compounds were isolated and identified as 2-chloropyridine (1), 70% yield, and 2-acetoxypyridine (2), 15% yield.[10]

We believe that the first step of the reaction is the complexation of the polar CH_2Cl_2 with the aromatic heteroatom. It has long been known that certain amines (e.g. Me_3N) react with dichloromethane forming *N*-(chloromethyl)ammonium salt in just a few hours.[11] Although

$$Me_3N + CH_2Cl_2 \rightarrow ClCH_2N^+Me_3 + Cl^-$$

with pyridine such a complete dissociation takes a very long time,[12] initial close approach of solvents of relatively high dipole moment can be fast. Such grouping is responsible for holding a partially negatively charged chlorine atom in the vicinity of the positive carbon of the *N*-fluorocarbocation A formed after the initial attack of the electrophilic fluorine on the nitrogen atom. This charged chlorine can then successfully compete with the acetoxy residue of the acetyl hypofluorite for the positive charge on C-2.[13]



With $CHCl_3$ or CCl_4 (both of lower polarity then CH_2Cl_2) there is no appreciable complexation with the pyridine ring and only exclusive formation of the acetoxy derivative **2** in high yield was observed. On the other hand, despite the bulky alkyl residue, *tert*-butyl chloride with its high dipole moment gives up to 20% 2-chloropyridine along with 60% of **2**.

With dibromomethane or methyl bromide replacing methylene chloride, we witnessed again a very similar and fast reaction resulting in 50–60% yield of 2-bromopyridine (**3**) along with about 20% of the acetoxy derivative **2**.

The above reaction is not confined to unsubstituted pyridine. 4-Methylpyridine in CH_2Cl_2 follows the same reaction pattern, forming 2-chloro-4-methylpyridine (**4**) in 60% yield, again accompanied by 20% of the corresponding acetoxy derivative **5**. Somewhat different results were obtained with pyridine rings substituted at the 3 position by an electron-withdrawing group. Reacting 3-chloropyridine in CH_2Cl_2 or CH_2Br_2 with AcOF gave the corresponding 2,3-dichloropyridine (**6**) and the unknown 2-bromo-3-chloropyridine (**7**) in 80% yield each. From 3-benzoylpyridine in CH_2Cl_2 2-chloro-3-benzoylpyridine (**8**) was produced, also in 80% yield. In all these cases only traces of the 2-acetoxypyridine could be detected. We believe that the reason for the excellent regioselectivity and for the almost complete absence of the 2-acetoxy derivative is the relative stability of the resulting *N*-fluorocarbocation at the 2 position. In addition to the stability this carbocation gains from the lone pair electrons of the nitrogen atom, there is also good overlapping of the nonbonding orbitals of the substituent at C-3 with the empty orbital at C-2.[14] The collapse of the ion pair is therefore retarded, improving the chance for the acetoxy anion to

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(2) While the work presented here was in its final stages, another work of somewhat similar nature has been reported: Umemoto, T.; Tomizawa, G. *Tetrahedron Lett.* **1987**, *28*, 2705.

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(8) Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* **1985**, *50*, 4753.

(9) For a somewhat similar role of CH_2Cl_2, see: Quarroz, D. Eur. Pat. 84118, 1983; *Chem. Abstr.* **1983**, *99*, 139791.

(10) In a typical reaction a $CFCl_3$ solution of AcOF, prepared according to ref 4, 6, and 8, was added dropwise at room temperature to a solution of the corresponding pyridine derivative (about 30 mmol) in 10–15 mL of the appropriate solvent. The reaction was instantaneous and monitored usually by TLC. About 1.2 to 1.5 mol/equiv of AcOF were needed for a complete conversion. The final products, both new and known, were chromatographically purified and their physical and spectroscopic data were in perfect agreement with the proposed structure as well as with either an authentic sample or with the data described in the literature.

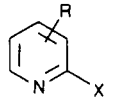
(11) Davies, W. C.; Evans, G. B.; Hulbert, F. L. *J. Chem. Soc.* **1939**, 412.

(12) Nevstad, G. O.; Songstad, J. *Acta Chem. Scand., Ser. B* **1984**, *38*, 469.

(13) It should be noted that the crucial step in Umemoto's interesting reaction (ref 2) is a base-induced proton abstraction from *N*-fluoropyridinium triflate producing a carbene intermediate. Such a mechanism cannot apply to reactions of acetyl hypofluorite which are conducted in acidic media. What is more, solvents such as THF are not incorporated in the pyridine ring in contrast to what was found in the carbene reactions.

(14) Similar reasoning has led to the proposal that cyclic halonium ions are responsible for the anti mode addition of chlorine or bromine to olefins.

diffuse out of the tight ion pair cage, so that the polarized solvent molecules will be the ones to react with the *N*-fluorocarbocation. It should be noted that while AcOF does not react with the chlorinated or the brominated solvents to produce free or anionic halogen, it oxidizes compounds such as MeI or CH_2I_2 to iodine and therefore no iodination of the pyridine ring could be achieved.[15]



4, R = 4-Me; X = Cl
5, R = 4-Me; X = OAc
6, R = 3-Cl; X = Cl
7, R = 3-Cl; X = Br
8, R = 3-COPh; X = Cl
9, R = H; X = OMe
10, R = H; X = OEt

While routes for direct halogenation, difficult as they might be, do exist, no direct methods for alkoxylation are known. Ethers are usually prepared through already derivatized rings. Acetyl hypofluorite provides an excellent opportunity to close this gap. Replacing the halogenated solvents with primary alcohols such as MeOH or EtOH resulted in an about 70% yield of 2-methoxy- and 2-ethoxypyridine (**9** and **10**), respectively, again accompanied by 15% to 20% of the acetoxylated derivative **2**.

In conclusion this work shows that elemental fluorine, that most neglected of reagents, can perform indirectly some very selective reactions leading to difficult to obtain fluorine-free compounds under incomparably mild conditions.

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Registry No. **1**, 109-09-1; **1** (X = H), 110-86-1; **2**, 3847-19-6; **3**, 109-04-6; **4**, 3678-62-4; **4** (X = H), 108-89-4; **5**, 108168-80-5; **6**, 2402-77-9; **6** (X = H), 626-60-8; **7**, 96424-68-9; **8**, 80099-81-6; **8** (X = H), 5424-19-1; **9**, 1628-89-3; **10**, 14529-53-4; AcOF, 78948-09-1; $CH_2(Cl)_2$, 75-09-2; *t*-BuCl, 507-20-0; $CH_2(Br)_2$, 74-95-3; MeBr, 74-83-9; MeOH, 67-56-1; EtOH, 64-17-5.

(15) For similar behavior of F_2 with halogenated compounds, see: Rozen, S.; Brand, M. *J. Org. Chem.* **1981**, *46*, 733.

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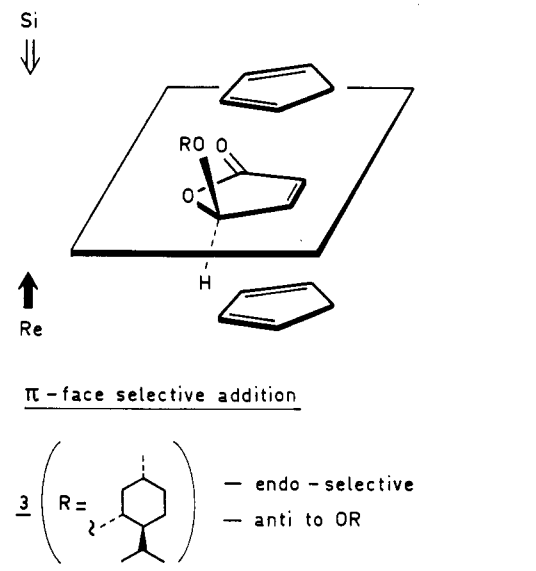
Asymmetric Diels–Alder Reactions with a Chiral Maleic Anhydride Analogue, 5-(1-Menthyloxy)-2(5*H*)-furanone

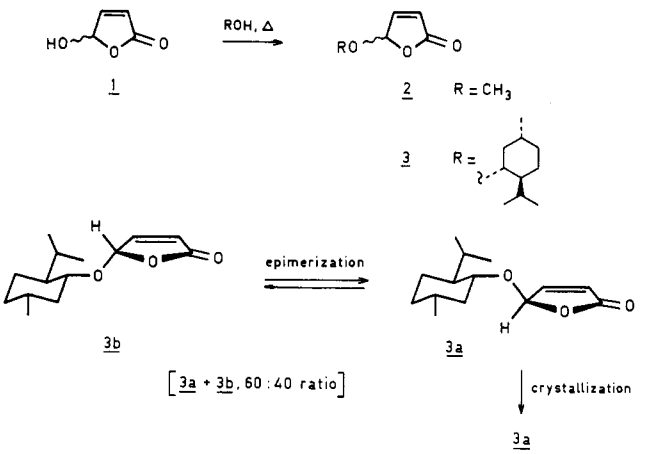
Summary: 5-(1-Menthyloxy)-2(5*H*)-furanone was used as a chiral dienophile in thermal asymmetric Diels–Alder reactions with several cyclic and acyclic dienes to give enantiomerically pure products.

Sir: The challenge of control of the absolute stereochemistry in Diels–Alder reactions[1] is evident from its prominent role in organic synthesis. Excellent diastereoselectivity has been achieved in Lewis acid catalyzed Diels–Alder reactions of chiral acrylates.[2,5] Modest to high asymmetric inductions were the result of cycloadditions using chiral catalysts,[3] chiral dienes,[4] or dienophiles.[1,2,5] However, the synthetic utility has been severely restricted by the scope of the asymmetric Diels–Alder reactions, the necessity of Lewis acid catalysis, or the accessibility of the chiral auxiliary. Only limited success has been reached in thermal asymmetric Diels–Alder reactions.[1,2] We have now developed a versatile synthetic route to enantiomerically pure Diels–Alder products using chiral maleic anhydride analogue synthons.

Scheme I



Scheme II



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