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Perfluoroalkylations

Condensed-Phase, Halogen-Bonded CF_3I and C_2F_5I Adducts for Perfluoroalkylation Reactions**

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Abstract: *A family of practical, liquid trifluoromethylation and pentafluoroethylation reagents is described. We show how halogen bonding can be used to obtain easily handled liquid reagents from gaseous CF_3I and CF_3CF_2I. The synthetic utility of the new reagents is exemplified by a novel direct arene trifluoromethylation reaction as well as adaptations of other perfluoroalkylation reactions.*

Fluorinated organic molecules are increasingly useful in medicinal chemistry, agrochemistry, and materials science. Many recent advances in fluoroorganic chemistry[1] are due to the development of safer, less toxic, or more selective reagents. Examples in perfluoroalkylation include the Ruppert–Prakash reagent (Me_3SiCF_3),[2] the Trifluoromethylator reagent (“CF_3Cu”),[3] the Langlois reagent (CF_3SO_2Na),[4] the Baran reagent $Zn(SO_2CF_3)_2$,[5] the Umemoto reagent (*S*-(trifluoromethyl)dibenzothiophenium),[6] and the Togni reagents.[7] Perfluoroalkyl iodides, in particular CF_3I,[8–14] are useful and inexpensive sources of perfluoroalkyl fragments.[1b,d,15] However, CF_3I and C_2F_5I are gases, making accurate measurement cumbersome. Stock solutions of CF_3I cannot be stored without quick decline of the titer (see the Supporting Information). Here we introduce liquid-phase, halogen-bonded adducts of CF_3I and C_2F_5I as perfluoroalkylation reagents. The reagents are stable at room temperature and can be conveniently manipulated. To the best of our knowledge, our report describes the first application of halogen bonding for organic reagent preparation, and the first X-ray crystal structure of a halogen-bonded CF_3I adduct. Using the easily manipulated halogen-bonded adducts, we have developed a novel direct arene C−H trifluoromethylation reaction. We also show the applicability of our new reagents as drop-in replacements for gaseous CF_3I and C_2F_5I.

Halogen bonding[16] has been known since 1863[17] and has found use in molecular recognition and supramolecular chemistry.[18] However, halogen bonding has received relatively little attention from synthetic organic chemists[9c,17j,19] compared to other non-covalent interactions such as hydrogen bonding. Trifluoromethyl iodide is a common trifluoromethylation reagent.[8–14] Despite its utility and low cost ($ 110 per mol from Oakwood Products), routine use by synthetic chemists has been challenging due to its boiling point of −22.5 °C. The handling process is impractical, time consuming, and imprecise in the measurements of small quantities, when compared to the other more conveniently handled reagents mentioned above.

We have found that CF_3I and tetramethylguanidine (TMG) form a 1:1 adduct that is liquid at 23 °C and can be dispensed accurately with a syringe (Figure 1). A 30 g batch of TMG·CF_3I stored in a glass vial with a Teflon seal at 0 °C showed no signs of decomposition, loss in content of CF_3I, or pressure build-up over two months. This reagent is now commercially available.[20] In addition to TMG, other Lewis bases can be used. Notably, the non-Brønsted-basic DMSO forms a 1:1 adduct with CF_3I. The presence of a second equivalent of DMSO imparts improved stability, making the preferred formulation 2 DMSO·CF_3I. Like CF_3I, C_2F_5I is a gas in most laboratory settings (bp 12–13 °C) and forms a readily handled liquid adduct with TMG. We found that TMG·CF_3CF_2I and DMSO·CF_3CF_2I can be used in analogy to TMG·CF_3I and DMSO·CF_3I as pentafluoroethylation reagents.

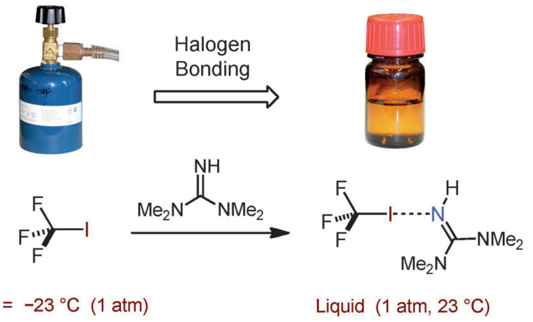

Figure 1. Formation of liquid TMG·CF_3I adduct via halogen bonding between CF_3I and tetramethylguanidine (TMG).

Trifluoromethylated arenes are increasingly common structural motifs in pharmaceuticals and agrochemicals.[21] Historically, trifluoromethyl arenes were synthesized via the Swarts reaction[22] or cross-coupling.[1e,15i,23] An attractive alternative to these methods is direct C−H trifluoromethylation by trifluoromethyl radical. Reagents such as $CF_3SO_2^-$ salts,[4,5] gaseous CF_3I,[8] CF_3SO_2Cl,[24a] $(CF_3)SiMe_3$,[24b–d] and Togni’s reagent[24e] have been used for this transformation. Some current methodologies are limited to specific substrate classes such as heterocycles, phenols, or anilines. Others

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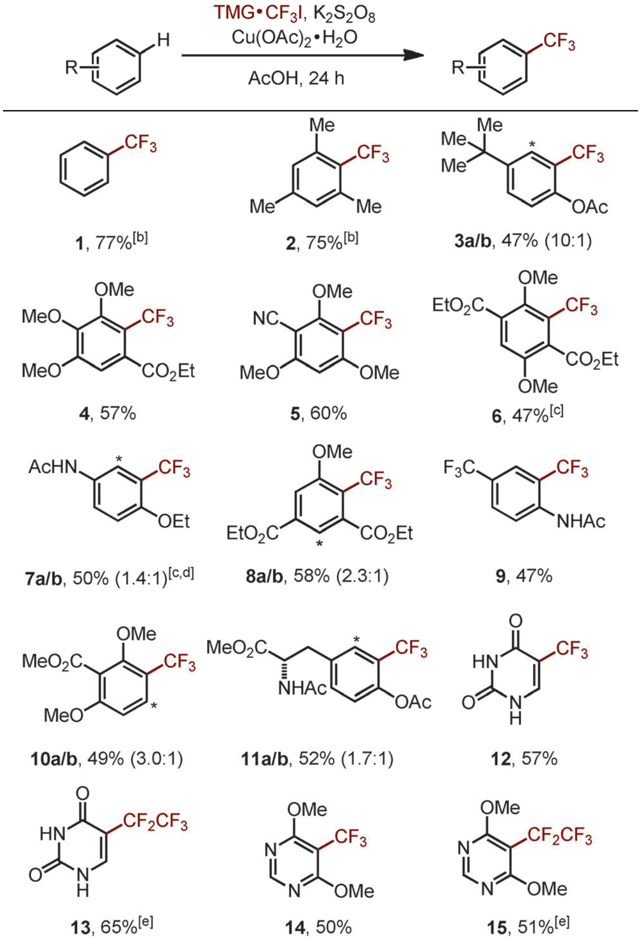
require the use of reagents that are gaseous or corrosive, or require special apparatus to perform. We have developed a method for C–H trifluoromethylation that does not suffer from these limitations.

Utilizing liquid TMG·CF_3I, we were able to rapidly optimize conditions for direct arene trifluoromethylation. We found that electron-neutral to electron-rich arenes could be directly trifluoromethylated when treated with TMG·CF_3I, $K_2S_2O_8$, and $Cu(OAc)_2·H_2O$ in acetic acid at 90 °C (Table 1).[25] The reactions are conducted under ambient atmosphere and with no need for rigorous exclusion of moisture or specialized equipment.

The reaction conditions are compatible with common arene substituents, including ethers, esters, nitriles, and amides. The reaction is also effective with highly substituted arenes and electron-deficient heterocycles. The reagent TMG·CF_3CF_2I can be substituted for TMG·CF_3I to afford pentafluoroethylated products. Positional selectivities are generally modest; generation of mixtures of positional isomers is common for direct arene trifluoromethylations.[4,5,8,24] Direct arene trifluoromethylation using TMG·CF_3I is an effective and operationally simple method made possible by the condensed-phase nature of the reagent.

Table 1: Direct perfluoroalkylation of arenes using halogen-bonded reagents.[a]



1, 77%[b]; **2**, 75%[b]; **3a/b**, 47% (10:1)

4, 57%; **5**, 60%; **6**, 47%[c]

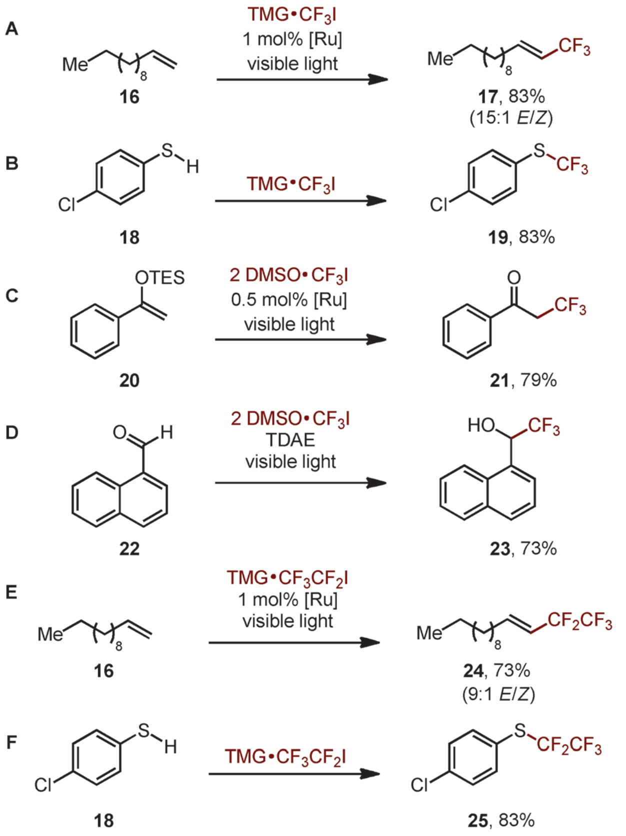
7a/b, 50% (1.4:1)[c,d]; **8a/b**, 58% (2.3:1); **9**, 47%

10a/b, 49% (3.0:1); **11a/b**, 52% (1.7:1); **12**, 57%

13, 65%[e]; **14**, 50%; **15**, 51%[e]

[a] Conditions: 2 equiv TMG·CF_3I, 4 equiv $K_2S_2O_8$, 2 equiv $Cu(OAc)_2·H_2O$, AcOH, 90 °C, 24 h. Yields of isolated products are shown unless otherwise specified. * indicates site of minor functionalization. [b] Yield determined by ^{19}F NMR spectroscopy. [c] Reaction conducted at 120 °C. [d] 4 equiv *t*BuOOH and 0.2 equiv $FeSO_4·7H_2O$ were utilized instead of $K_2S_2O_8$ and $Cu(OAc)_2·H_2O$. [e] TMG·CF_3CF_2I was utilized instead of TMG·CF_3I.

To further demonstrate the synthetic utility of TMG·CF_3I, we have explored its use as a drop-in replacement for gaseous CF_3I (Scheme 1). TMG·CF_3I can be used in Stephenson's photoredox-catalyzed oxidative olefin trifluoromethylation (Scheme 1 A).[9b,e] Likewise, thiol trifluoromethylation can be accomplished with TMG·CF_3I (Scheme 1 B). In both cases, TMG acts as a base in addition to providing a liquid source of CF_3I.



16; **17**, 83% (15:1 *E*/*Z*)

18; **19**, 83%

20; **21**, 79%

22; **23**, 73%

16; **24**, 73% (9:1 *E*/*Z*)

18; **25**, 83%

Scheme 1. Representative perfluoroalkylation reactions using halogen-bonded reagents. [Ru] = $[Ru(bipy)_3]Cl_2·6H_2O$. TDAE = tetrakis(dimethylamino)ethylene.

In other cases, we found the presence of TMG to be detrimental. For example, TMG·CF_3I was not a suitable CF_3I surrogate for the MacMillan trifluoromethylation of enol ethers under photoredox catalysis.[11h] However, 2 DMSO·CF_3I proved effective both in the MacMillan trifluoromethylation and in the TDAE-mediated trifluoromethyl addition to aldehydes (Scheme 1 C and D, respectively). The ability of tetramethylguanidine to serve as one-electron reductant and/or H-atom donor may explain the differing reactivity of DMSO·CF_3I and TMG·CF_3I. We have also found that TMG·CF_3CF_2I is effective for pentafluoroethylation (Scheme 1 E and F).

To better understand our new reagents, we investigated the bonding in greater detail. The 1:1 stoichiometry of TMG·CF_3I was established by integration of the ^1H and ^{19}F NMR signals against a 1-fluoro-3-nitrobenzene standard. When approximately 5 equivalents of CF_3I were condensed into a known amount of TMG at −23 °C, and the reaction mixture was warmed to 23 °C, CF_3I evaporated until a 1:1 liquid adduct (TMG·CF_3I) was formed. The experiment is consistent with a well-defined 1:1 adduct.

We were unable to characterize TMG·CF_3I by X-ray crystallography, but we obtained crystals of the TMEDA analog (Figure 2 A). While the TMEDA·2 CF_3I adduct behaves similarly to the TMG·CF_3I adduct (see the Supporting Information), the TMEDA-based crystalline solid became sticky with storage, making it less practical to handle than TMG·CF_3I. The iodine–nitrogen interaction, which we ascribe to halogen bonding, was unambiguously established by measuring an interatomic N···I distance of 2.80 Å, smaller than the sum of the van der Waals radii for N and I (3.53 Å). DFT calculations corroborated the experimentally determined N···I distance. With the validated DFT functionals, we found an N···I distance of 2.8 Å for TMG·CF_3I, and an interaction energy corrected for basis set superposition error (BSSE) of 9–10 kcal mol^{-1}, near the upper end of the 1–10 kcal mol^{-1} range for halogen bond strength.[18j] The calculated halogen bond strength is consistent with the temperature and storage stability of TMG·CF_3I.

Halogen bonding can be rationalized as a non-covalent polar interaction between halogen bond donors, such as CF_3I, and halogen bond acceptors, such as TMG.[18h,i] The three filled lone pairs on iodine are almost purely s- and p-based orbitals, with little hybridization (Figure 2 C); the C–I σ-bond has p_z character on iodine, and is polarized toward the electron-withdrawing CF_3 group. Thus, minimal electron density is observed in the outermost region of the iodine atom along the z axis of the C–I σ-bond; this region has been named the σ-hole[26] (Figure 2 D). The attractive interaction between a Lewis base such as TMG and the σ-hole contributes to halogen bonding.[18h,i]

In conclusion, we have described the first use of halogen bonding to access reagents for organic synthesis. Stable, readily handled liquid adducts of CF_3I and CF_3CF_2I were prepared and used in perfluoroalkylation reactions. Using TMG·CF_3I, a novel arene C–H trifluoromethylation reaction has been developed. Given the strong interest in fluoroorganic compounds and perfluoroalkylation reagents, we anticipate that our reagents will be of use to the community both in wider accessibility of the rich chemistry of CF_3I and in development of novel reactions.

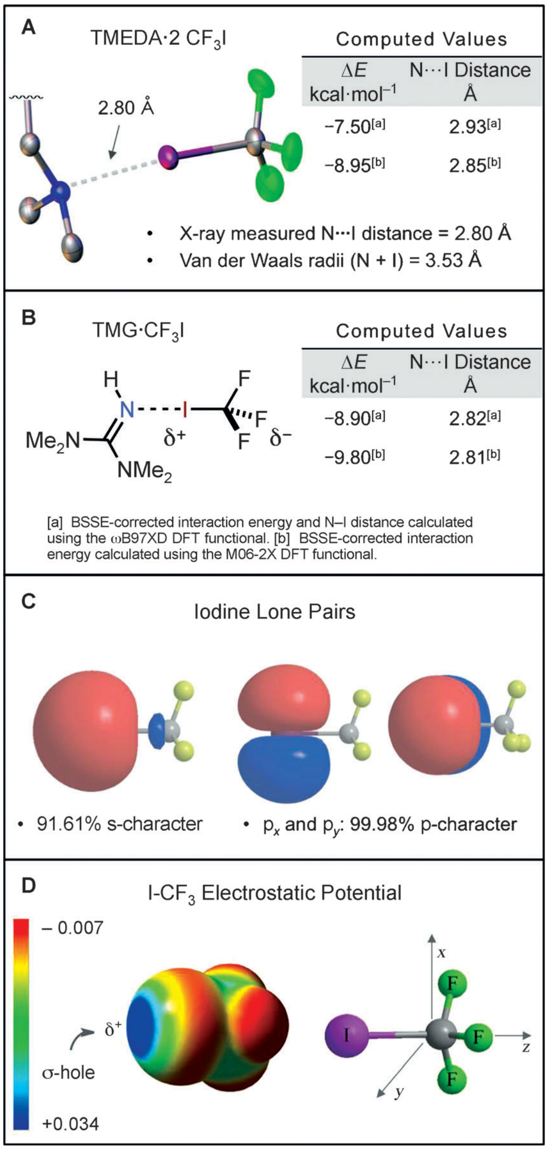


Figure 2. A) X-ray structure of TMEDA·2 CF_3I; experimentally measured and calculated N···I distance; calculated interaction energy per CF_3I molecule. B) Calculated interaction energy and N···I distance for TMG·CF_3I. C) The two p-type and the s-type iodine lone pairs in CF_3I. D) Electrostatic potential map of CF_3I (in Hartrees) at the 0.001 electrons Bohr^{-3} isodensity surface highlighting the σ-hole region. See the Supporting Information for details on the DFT calculations.

Experimental Section

General procedure for direct trifluoromethylation of arenes: Arene (0.250 mmol, 1.00 equiv), $K_2S_2O_8$ (270 mg, 1.00 mmol, 4.00 equiv), and $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.500 mmol) were dissolved in glacial acetic acid (2.0 mL). TMG·CF_3I (0.100 mL, 0.500 mmol, 2.00 equiv) was added, the reaction vessel was sealed and heated to 90 °C for 24 h. The reaction mixture was diluted with saturated aqueous Na_2CO_3 (50 mL) and the resulting mixture extracted with ethyl acetate (3 × 25 mL). The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on silica gel.

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Keywords: arenes · C–H functionalization · halogen bonding · pentafluoroethylation · trifluoromethylation

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Communications

Perfluoroalkylations

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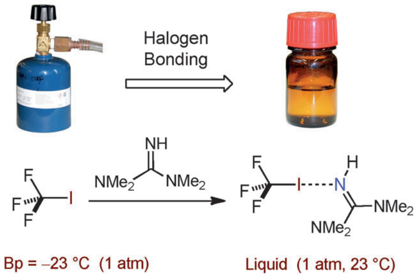
Condensed-Phase, Halogen-Bonded CF_3I and C_2F_5I Adducts for Perfluoroalkylation Reactions



It's (no longer) a gas! A family of practical, liquid trifluoromethylation and pentafluoroethylation reagents enabled by halogen bonding is described. The synthetic utility of these reagents is exemplified by a novel direct arene trifluoromethylation reaction as well as adaptations of other perfluoroalkylation reactions.