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Technical Note

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A Scalable Preparation and Thermal Analysis of Pentafluorophenyl Iodine(III) Diacetate

Abstract

Pentafluorophenyl iodine(III) diacetate (F_5-PIDA) is an electron-deficient hypervalent iodine(III) reagent with growing utility in modern synthetic methodology, including iodine(III)-mediated ring-expansion chemistry. However, its application as a stoichiometric reagent requires reliable access to preparative amounts. This article describes a practical chromatography-free protocol for the preparation of F_5-PIDA on a *ca.* 300 g scale by the oxidation of pentafluoroiodobenzene with sodium hypochlorite pentahydrate in acetic acid. The product was isolated by a simple slurry trituration in the hexane/MTBE mixture giving F_5-PIDA in the yield of 65 % and the purity of ≥ 98 %. The thermogravimetry-differential thermal analysis has shown that F_5-PIDA is stable up to approximately 100–110 °C, while the rapid decomposition occurs above this temperature range. The protocol developed provides a reliable preparative access to high-purity F_5-PIDA and practical thermal data for its safe use.

Keywords: hypervalent iodine; λ^3-iodane; scale-up; semi-industrial method; F_5-PIDA

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Масштабований синтез і термічний аналіз пентафлуорофенілйод(III) діацетату

Анотація

Пентафлуорофенілйод(III) діацетат (F_5-PIDA) є електронодефіцитним реагентом йоду(III), що набуває дедалі більшого значення в сучасній синтетичній методології, зокрема в реакціях розширення циклу. Однак його застосування як стехіометричного реагенту потребує надійного доступу до препаративних його кількостей. У цій роботі описано практичний протокол одержання F_5-PIDA в масштабі *ca.* 300 г шляхом окиснення пентафлуоройодобензену натрій гіпохлоритом пентагідратом в оцтовій кислоті без використання хроматографічного очищення. Продукт було виділено шляхом простої тритурації в суміші гексан/МТВЕ з виходом 65 % і чистотою ≥ 98 %. Термогравіметричний / диференційно-термічний аналіз показав, що F_5-PIDA є стабільним без суттєвої втрати маси до приблизно 100–110 °С, тоді як вище цього температурного діапазону відбувається швидкий розклад. Розроблений протокол забезпечує надійний препаративний доступ до високочистого F_5-PIDA і надає практичні термічні дані для його безпечного використання.

Ключові слова: гіпервалентний йод; λ^3-йодан; масштабування; напівіндустріальний метод; F_5-PIDA

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■ Introduction

Hypervalent iodine(III) reagents have become important tools in modern organic synthesis since they combine a strong oxidizing ability with operational simplicity, broad functional-group tolerance, and metal-free reaction conditions [1–3]. A recent comprehensive review reveals them as unique reagents enabling transformations that cannot be performed by using any other common, non-iodine-based chemical [1]. According to the review, [*bis*(acyloxy)iodo]arenes constitute a highly important family of hypervalent iodine reagents, which broad synthetic utility has been extensively covered in numerous review articles [4–6]. Among them, (diacetoxyiodo)arenes, $ArI(OAc)_2$, are especially useful oxidants and electrophilic group-transfer reagents, and their reactivity can be tuned by changing the electronic nature of the aryl substituent attached to the iodine(III) center. Notably, SciFinder® returns over 2,400 publications describing synthetic applications of the parent reagent, (diacetoxyiodo)benzene (PIDA, $PhI(OAc)_2$), that appeared between 2016 and 2025. Electron-deficient aryl iodine(III) reagents are of particular interest as they can effectively tune the reactivity profile of the common PIDA reagent [7–10]. In this regard, pentafluorophenyl iodine(III) diacetate ($C_6F_5I(OAc)_2$, F_5-PIDA) represents a useful fluorinated analog of PIDA, in which the strongly electron-withdrawing pentafluorophenyl group increases the electrophilic character of the iodine(III) center. This feature can be decisive in transformations where the electronic properties of the hypervalent iodine reagent control the reaction pathway. A recent example is the iodine(III)-mediated ring expansion of exocyclic alkenes to saturated *gem*-difluorinated rings [11]. In this study, tuning the electronic properties of the aryl iodine(III) reagent was shown to be critical, and electron-rich analogs favored the undesired vicinal difluorination, while electron-poor reagents promoted the desired ring-expansion pathway. F_5-PIDA was identified as the optimal reagent, enabling an efficient formation of saturated *gem*-F_2-rings and suppressing competing side processes. This result highlighted the synthetic value of F_5-PIDA and created a practical need for the reliable access to this reagent in preparative quantities.

The synthesis of F_5-PIDA from pentafluoroiodobenzene using sodium hypochlorite pentahydrate in acetic acid was previously reported by *Watanabe and co-workers* as part of a general safer protocol for the preparation of (diacetoxyiodo)arenes [12]. The method is attractive since $NaClO \cdot 5H_2O$ is an inexpensive, nonexplosive oxidant and avoids the use of hazardous oxidants, such as peracetic acid or chromium-based systems. However, the preparation of F_5-PIDA in that work was demonstrated only on a 2 mmol scale, giving approximately 0.7 g of the product.

For a broader synthetic use, especially in reactions where F_5-PIDA is required as a stoichiometric reagent, the sub-gram access is insufficient. A practical scale-up must address not only the conversion, but also operational safety, reproducibility, product isolation, and avoidance of the chromatographic purification. Herein, we describe a reproducible chromatography-free preparation of high-purity F_5-PIDA on a *ca.* 300 g scale from pentafluoroiodobenzene using sodium hypochlorite pentahydrate as an oxidant. In addition, the thermogravimetric analysis of the material obtained is presented to determine its thermal stability profile and provide practical guidance for handling this reagent on a preparative scale.

■ Results and discussion

The oxidation of pentafluoroiodobenzene to F_5-PIDA was selected as the target transformation for scale-up studies. The original procedure reported by *Watanabe and co-workers* [12] demonstrated that sodium hypochlorite pentahydrate is an efficient and relatively safe oxidant for the conversion of a broad range of iodoarenes into the corresponding (diacetoxyiodo)arenes. In that work, pentafluoroiodobenzene was successfully oxidized on a 2 mmol scale to give F_5-PIDA in high purity. However, larger-scale preparation was demonstrated only for the parent PIDA derived from iodobenzene. Therefore, direct extrapolation to multihundred-gram quantities of F_5-PIDA required additional practical validation.

At the outset, we aimed to preserve the simplicity of the original oxidation system while adapting it for the preparative-scale operation. Sodium hypochlorite pentahydrate was chosen as the oxidant since it provides a high effective concentration of active hypochlorite and avoids the large excess of water associated with aqueous sodium hypochlorite solutions. This feature is particularly important as aqueous hypochlorite can promote the overoxidation to iodine(V) species in related systems [12]. Acetic acid was retained as both the reaction medium and the acetate source, enabling a direct formation of the diacetoxyiodo product.

On scale-up, several operational parameters were adjusted (**Scheme 1**). Instead of adding pentafluoroiodobenzene in one portion, it was introduced gradually to a stirred suspension of sodium hypochlorite pentahydrate in acetic acid. This modification provided better control over mixing and the local reagent concentration. The reaction time was also slightly extended relative to the small-scale procedure to ensure the complete conversion under preparative conditions. After the completion of the oxidation, the reaction mixture was diluted with dichloromethane, and the inorganic residues were removed by the filtration. The organic phase was dried and concentrated to give a crude product.

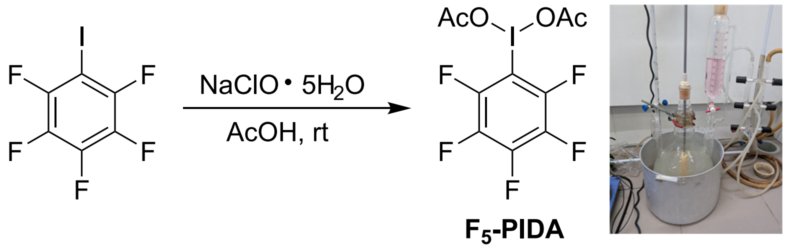
A key practical issue was the isolation of F_5-PIDA in high purity without the chromatographic purification or additional chemical treatment. In the general procedure previously reported, the purification of some (diacetoxyiodo)arenes could involve the recrystallization, treatment with acetic anhydride, or other post-reaction operations. For the multihundred-gram synthesis, these options are less convenient. We found that simple slurry trituration of the crude material in the hexane/MTBE mixture (9:1) was sufficient to remove impurities and give F_5-PIDA as a white solid with the purity of ≥ 98%, as determined by the GC-MS and NMR analysis. This purification was operationally simple and avoided the need for the column chromatography. Under these conditions, F_5-PIDA was obtained reproducibly in the isolated yield of 62–65% as an analytically pure solid suitable for further synthetic use.

Under the optimized preparative conditions, pentafluoroiodobenzene was converted to F_5-PIDA on a *ca.* 300 g scale in a single run. The target reagent was isolated as a white crystalline solid weighing 273.2 g, corresponding to the yield of 65%. The product identity was confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and the GC-MS analysis. The material obtained was suitable for further synthetic use, including iodine(III)-mediated ring-expansion reactions of exocyclic alkenes to saturated *gem*-difluorinated rings, for which F_5-PIDA had previously been identified as the optimal reagent [11].

The thermal behavior of the isolated F_5-PIDA was examined by the TG/DTA/DTG analysis in the temperature range from room temperature to 500 °C (**Figure 1**). The TG curve showed no significant mass loss below approximately 100–110 °C, indicating the absence of substantial amounts of volatile impurities or a residual solvent and suggesting that the material can be handled at ambient temperature without a detectable thermal degradation. A rapid mass loss began at approximately 120–130 °C, followed by the main decomposition event in the range of 130–190 °C. The DTG curve displayed a sharp maximum at approximately 150–160 °C, corresponding to the highest rate of the mass loss. The DTA signal showed a thermal event in the same temperature region, consistent with the rapid decomposition of the hypervalent iodine(III) reagent. Above 200 °C, only a slow additional decrease in mass was observed, and the final residue at 500 °C accounted for approximately 1–3% of the initial sample mass. The data show that F_5-PIDA possesses a defined thermal stability window but undergoes the rapid decomposition shortly after the onset temperature. Although the reagent is sufficiently stable for routine handling and storage under appropriate conditions, exposure to elevated temperatures should be avoided during drying, concentration, storage, or further synthetic use.

■ Conclusion

A practical protocol for the multihundred-gram synthesis of pentafluorophenyl iodine(III) diacetate (F_5-PIDA) has been developed. The oxidation of 300 g of pentafluoroiodobenzene with sodium hypochlorite pentahydrate in acetic acid gave 273.2 g of F_5-PIDA, with the isolated yield of 65% and the purity of ≥ 98%, as determined by the GC-MS and NMR analysis. The procedure avoids



- scale-up to *ca.* 300 g
- *65 %* isolated yield
- purity ≥ 98 %
- chromatography-free isolation protocol
- simple purification
- thermal stability profile

Scheme 1. The synthetic outline and distinct features of the protocol

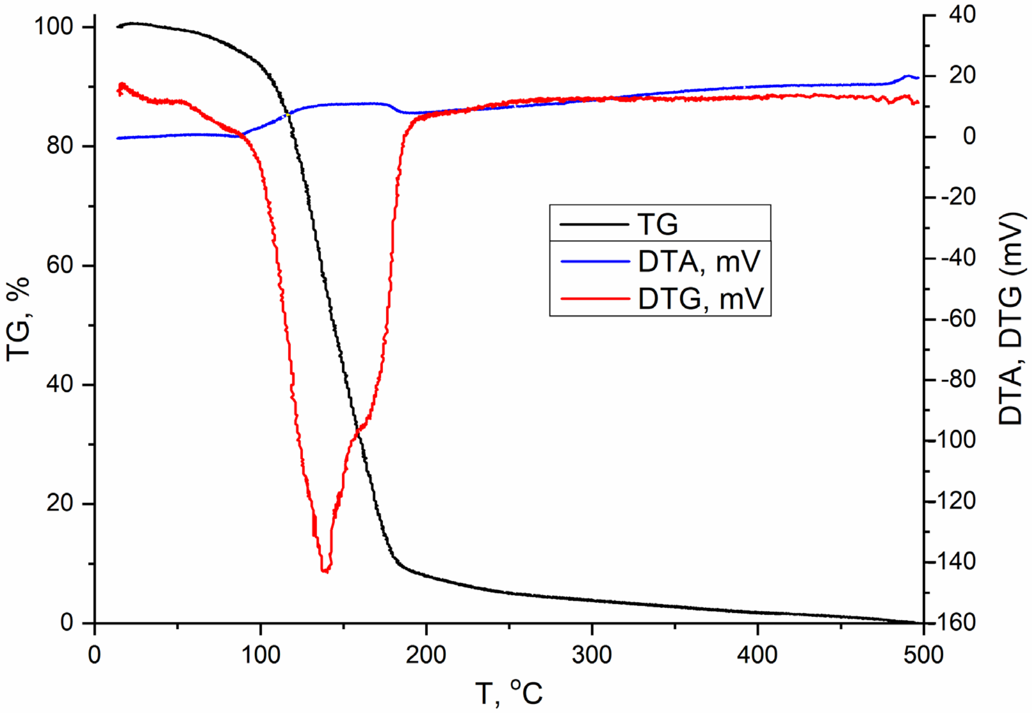


Figure 1. The TG/DTA/DTG analysis of F_5-PIDA

the chromatographic purification and relies on a simple slurry trituration in hexane/MTBE, making it convenient for the preparative-scale use. The preparation of sodium hypochlorite pentahydrate is also included to standardize the overall protocol and improve the reproducibility of the oxidation step. The TG/DTA/DTG analysis has shown that F_5-PIDA is stable without a significant mass loss up to approximately 100–110 °C, while the rapid decomposition occurs above this range, with the main mass-loss event between approximately 130 and 190 °C. These results provide practical guidance for handling and processing the reagent.

■ Experimental part

All regents used were taken from Enamine Ltd stock. Analytical TLC was performed using Polychrom SI F254 plates. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 AVANCE 500 instrument (500 MHz for ^{1}H and 126 MHz for ^{13}C), ^{19}F NMR spectra were obtained on a Varian Unity Plus 400 (376 MHz) spectrometer. GCMS analyses were performed using an Agilent 5890 Series II 5972 GCMS instrument [electron impact (EI) ionization (70 eV)], respectively.

The Preparation of Sodium Hypochlorite Pentahydrate ($NaClO{\cdot}5H_2O$)

Caution: *Chlorine is a toxic and corrosive gas. All operations involving chlorine were performed in a well-functioning fume hood using the appropriate gas-handling and scrubbing equipment. Sodium hypochlorite pentahydrate is a strong oxidant and should be handled with the appropriate protective equipment, avoiding contact with organic materials, acids, reducing agents, and heat.*

Sodium hydroxide (500 g) was dissolved in water to prepare a 45 wt% aqueous NaOH solution (1.11 kg total). The solution was placed in a polypropylene reactor equipped with efficient mechanical stirring and external cooling. Chlorine gas was introduced at a controlled rate while maintaining the internal temperature at 25–30 °C. The amount of chlorine introduced corresponded to approximately 429 g of Cl_2.

After the completion of the chlorine addition, the resulting suspension was filtered through a polypropylene frit to remove precipitated sodium chloride. The filtrate was transferred to a polypropylene vessel, cooled to 12 °C, seeded with sodium hypochlorite pentahydrate from the previous preparation (*ca.* 4 g), and maintained at this temperature for 2 days. The crystals formed were collected by the filtration and stored at 4 °C.

The first preparation performed without seeding gave a significantly lower yield. The second crystallization of the mother liquor was also possible. However, the resulting material showed lower activity and reduced stability. Therefore, to prepare F_5-PIDA, freshly crystallized first-crop sodium hypochlorite pentahydrate was used. The remaining mother liquor was used in other oxidative transformations. This preparation was adapted from the reported patent procedure for crystalline sodium hypochlorite pentahydrate [13].

The Preparation of Pentafluorophenyl Iodine(III) Diacetate (F_5-PIDA) on a 300 g Scale

A suspension of sodium hypochlorite pentahydrate ($NaClO \cdot 5H_2O$, 415.8 g, 2.00 equiv) in glacial acetic acid (2.50 L) was prepared in a glass reactor equipped with mechanical stirring. Pentafluoroiodobenzene (300.0 g, 1.00 equiv.) was added over 10 min at room temperature. The reaction mixture was stirred at room temperature for approximately 15 min and then diluted with dichloromethane (3.0 L). The inorganic material was removed by the filtration, and the organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude solid was triturated with hexane/MTBE (9:1) to give pentafluorophenyl iodine(III) diacetate (F_5-PIDA) as a white solid with the purity of ≥ 98%, as determined by GC-MS and NMR.

A white solid. Yield – 273.2 g (65%). M. p. 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.00 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 178.4, 146.9–146.5 (m), 146.2–145.3 (m), 144.9–144.4 (m), 144.1–143.4 (m), 138.6–138.1 (m), 136.6–136.1 (m), 96.2 (dt, J = 27.1, 4.7 Hz), 20.1. ^{19}F NMR (376 MHz, $CDCl_3$), δ, ppm: -121.5 (m), -144.1 (m), -157.0 (m). GCMS, m/z (EI): 293.9 $[M\text{-}2Ac]^+$.

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