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A Novel Method of Iodination and Azo Bond Formation by Nitrogen Triiodide †

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Abstract: A practical and green method for utilizing nitrogen triiodide on a multi-gram scale is presented. Nitrogen triiodide, known for its use in chemistry demonstrations due to its contact explosive properties, has had limited application in organic synthesis or industry until now. The described method allows for in-situ formation and safe use of nitrogen triiodide in iodination and azo bond formation with pyrazole derivatives. Iodination is achieved using one equivalent of iodine (or two-thirds equivalent of nitrogen triiodide), while azo bond formation is accomplished with an excess of iodine in the reaction mixture. Prepared compounds were characterized by detailed NMR analysis.

Keywords: nitrogen triiodide; iodination; azo compounds; pyrazoles

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1. Introduction

There exists a wide variety of iodinating reagents [1] and commonly utilized iodination reactions [2,3], including molecular iodine or potassium iodide paired with oxidation agents, pure N-iodosuccinimide, either alone or activated by a Lewis acid, and N-iodosaccharin. Indirect iodination methods also exist, such as a sequence involving deprotonation with butyllithium followed by anion trapping with iodine, the Sandmeyer reaction via diazonium salts, or the Finkelstein reaction involving the exchange of bromine for iodine in aromatic derivatives. However, none of these methods is universally applicable to a broad range of substrates due to several drawbacks, including the need for strong oxidizing agents, chlorinated solvents, toxic reagents, multi-step synthesis, or conditions sensitive to air or moisture. Additionally, some iodinating reagents suffer from poor atom economy. Consequently, there is a need for the development of a complementary iodination method that can address some of these challenges.

Nitrogen triiodide is a well-known contact explosive often used in chemistry demonstrations and educational outreach. This inorganic compound has a complex structure, $[NI_3.NH_3]n$ or $[NI_3.(NH_3)_3]n$, depending on whether the starting materials are molecular iodine and ammonia [4]. Pure NI_3 can be synthesized by reacting boron nitride with iodine monofluoride in $CFCl_3$ at −30 °C [5]. The properties and stability of all nitrogen trihalides have been extensively studied in the past. Nitrogen triiodide can undergo explosive decomposition at 0 °C and has a very low detonation threshold, particularly when in a dry state. As a result, it currently has almost no industrial or synthetic applications. However, its decomposition can be slowed down by the presence of ammonia, water, and increased pressure over the solid [6]. Building on this knowledge, we developed a method for utilizing nitrogen triiodide in organic synthesis, from its in-situ formation to the disposal of

residues in ethanol. Moreover, the entire process is conducted in an aqueous solution at room temperature to minimize potential risks.

Although, the main driving force for the development of novel iodination/azo bond formation methods is significant utility of iodinated organic compounds, which can serve as versatile building blocks in organic synthesis [7], particularly in C–C and N–C coupling reactions such as the Sonogashira, Stille, Buchwald, and Heck reactions. Aryl iodides are also used in the synthesis of hypervalent iodine compounds, which form a distinct category in chemistry. These hypervalent iodine compounds can exist in oxidation states III [8] or V [9], enabling them to facilitate further iodination, oxidation reactions, and cyclization processes. Many iodinated organic molecules possess bioactive properties [10], such as acting as indirect antagonists of the thyroid hormone receptor [11] or exhibiting antiparasitic activity against Trypanosoma cruzi, which is used to treat the chronic form of Chagas disease [12]. Additionally, the decay of iodine radioisotopes allows iodinated aryl compounds to be used as imaging agents in positron emission tomography (PET) and single photon emission computed tomography (SPECT) [13].

Azo compounds have historically been used as dyes and drugs, but in recent years, their application as photoswitches and photosensitizers has been steadily increasing due to their ability to efficiently and controllably isomerize between the E and Z forms of the N=N double bond [14]. This isomerization is typically induced by irradiation with specific wavelengths of light, although heat or pH changes can also serve as activators. The two isomeric forms possess different physical and pharmacological properties, which makes these compounds promising for use in optoelectronics, targeted drug delivery, photodynamic therapy, energy storage, optical storage, and more. Generally, the E isomers are thermodynamically more stable than the Z isomers, and to fully harness the potential of the Z isomers, it is crucial to have a long half-life of isomerization following the initial irradiation. Among azo compounds, azo pyrazoles stand out for having one of the longest recorded isomerization half-lives, reaching up to 1000 days [15]. These factors collectively drive the need for more cost-effective, environmentally friendly, efficient, and robust iodination methods that allow for selective azo bond formation

2. Material and Methods

NMR spectra were obtained using two NMR spectrometers: Varian 400 MR spectrometer (operating frequencies 400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F, equipped by an AutoX dual broadband probe) and Bruker 400 MHz spectrometer. The chemical shift scales were calculated using the reference frequencies of tetramethylsilane (TMS) for ^{1}H and ^{13}C. If present, the ^{1}H and ^{13}C signal of TMS was used to correctly shift the ^{1}H and ^{13}C chemical shift scales. Alternatively, the signals of the used solvents were used as secondary standards (^{1}H: $CHCl_3$—7.16 ppm, d_5-DMSO—2.50 ppm; ^{13}C: $CDCl_3$—77.160 ppm, DMSO-d_6—39.52 ppm). The ^{19}F chemical shift scale was correctly shifted using an automatic referencing mechanism exploiting the ^{2}H signal of the deuterated solvent.

The melting points were measured on a Boetius apparatus (Nagema, Radebeul, Germany) using a high-precision thermometer TD 121 from VWR. M.P. was left uncorrected.

3. Results and Discussion

3.1. Synthesis

The general iodination procedure is highly convenient and yields excellent results. It is conducted in a one-pot process at room temperature, using a green solvent (water), with good conversion typically achieved in minutes up to one hour for iodination and up to eight hours for azo bond formation. The method is effective for iodinating various pyrazole derivatives (Figure 1) and holds potential for broader application to other derivatives. All the derivatives produced were isolated from the reaction mixture by either extraction (for iodination) or by precipitation (for azo bond formation) as products sufficient purity

to be clearly identified by NMR without the need for further purification. Any potentially unreacted nitrogen triiodide can be safely neutralized by adding sodium thiosulfate to the reaction mixture after completion, as monitored by TLC. However, in our experiments, no unreacted nitrogen triiodide was detected, even when sodium thiosulfate was omitted during work-up.

If the iodinated structure contains amino groups, it may undergo coupling reactions to form azo groups under certain iodination conditions involving oxidizing reagents [16,17]. In the synthesis presented here, this can be selectively achieved by using an excess of nitrogen triiodide in the reaction mixture (Figure 2).

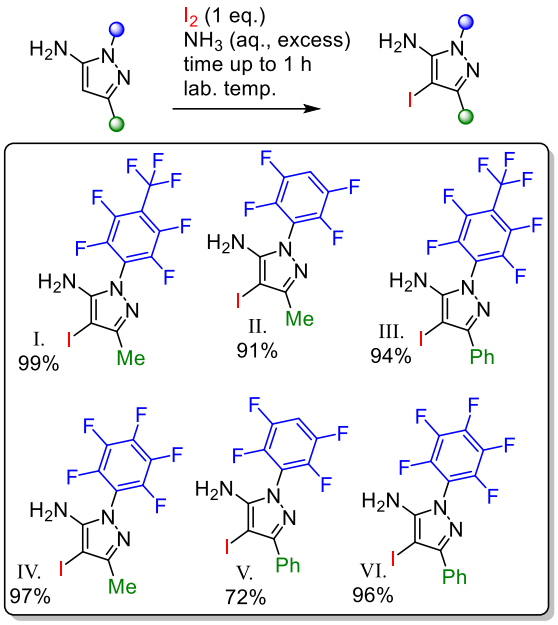

Figure 1. Synthesis of iodinated pyrazole series.

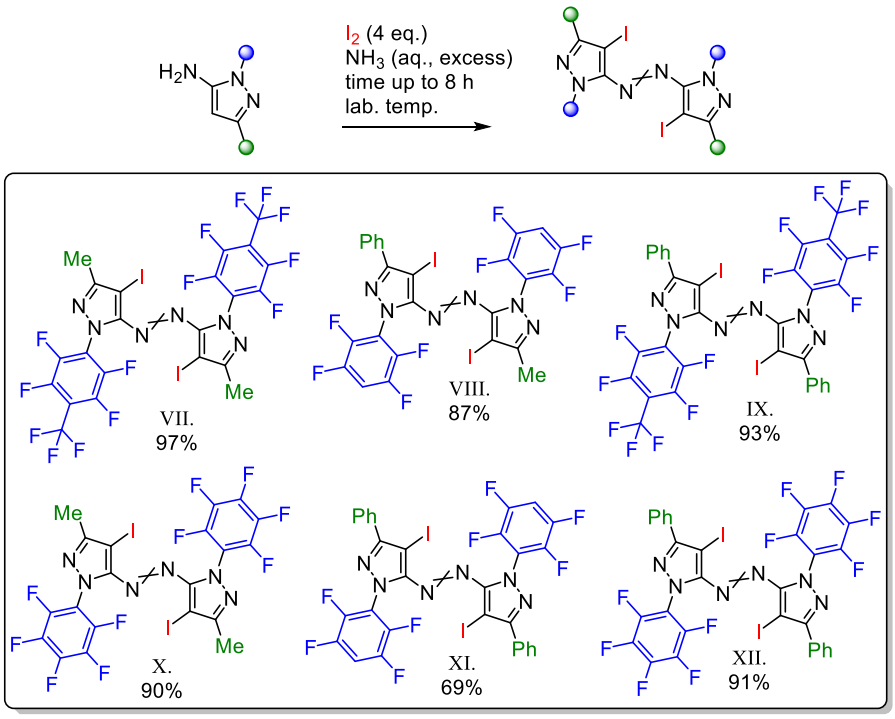

Figure 2. Synthesis of azo pyrazole series.

3.2. General Prcedure

In 250 mL flask is mixed iodine (1 eq.; 10 mmol; 2,5 g) with acetonitrile (50 mL), and subsequently 23–26% water solution of ammonia (50 mL) is added. In this manner, nitrogen triiodide is prepared in-situ. To the solution of nitrogen triiodide, a substrate (1 eq.; 20 mmol) is added, and the reaction mixture is stirred at room temp. The reaction is monitored by TLC, and the conversion usually stops within 1 h for iodination and within 8 h for azo bond formation. Sodium thiosulphate (1 eq.; 20 mmol) may be added into the reaction mixture to eliminate the residual nitrogen triiodide. Reaction mixture is evaporated under reduced pressure, and subsequently the organic part of the mixture is extracted into ethyl acetate (3 × 50 mL). Combined organic parts are dried over sodium sulphate and evaporated under reduced pressure to give a crude product of sufficient purity to be analyzed by NMR spectroscopy. In this manner a series of iodinated pyrazole derivatives is prepared.

The procedure for the azo bond formation is almost identical for iodination. There are three differences. First, an excess of starting iodine is used, specifically 4 equivalents of iodine (40 mmol; 10 g). Second, the reaction time is 8 h at room temperature. Third, the product is not extracted to ethyl acetate, but it will precipitate out of reaction mixture as insoluble solid within 8 h. The melting points, appearance of the products, and NMR data are listed in Table 1.

Table 1. This is a table. Tables should be placed in the main text near to the first time they are cited.

Compound	Melting Point /Appearance	NMR [2]
I	127–129 °C (EA [1]) /white solid	^{1}H NMR (400 MHz, DMSO-d6) δ 5.86 (s, 2H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 150.7, 148.4, 67.8, 17.1. ^{19}F NMR (376 MHz, DMSO-d6) δ −55.63 (t, J = 21.5 Hz, 3F), −141.56 (dddd, J = 35.0, 21.6, 13.5, 7.2 Hz, 2F), −143.6 (m, 2F).
II	155–158 °C (EA) /yellow solid	^{1}H NMR (400 MHz, DMSO-d6) δ 7.16 (m, 1H), 4.98 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 151.9, 149.4, 67.4, 17.4. ^{19}F NMR (376 MHz, DMSO-d6) δ −136.21 (m, 2F), −146.66 (m, 2F)
III	211–214 °C (EA) /white solid	^{1}H NMR (400 MHz, DMSO-d6): δ = 7.77 (m, 2H), 7.48 (m, 2H), 7.39 (m, 1H), 6.01 (s, 2H) ^{13}C NMR (100 MHz, DMSO-d6) δ 154.6, 150.6, 133.1, 129.5, 128.7, 128.4, 65.1. ^{19}F NMR (376 MHz, DMSO-d6) δ −55.42 (m, 3F), −140.35 (m, 2F), −142.11 (m, 2F).
IV	138–140 °C (EA) /yellow solid	^{1}H NMR (400 MHz, DMSO-d6) δ 5.75 (s, 2H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 151.7, 149.4, 65.9, 16.8. ^{19}F NMR (376 MHz, DMSO-d6) δ −145.66 (m, 2F), −154.12 (t, J = 22.8 Hz, 1F), −162.57 (m, 2F)
V	196–199 °C (EA) /orange solid	^{1}H NMR (400 MHz, DMSO-d6) δ 7.73 (m, 2H), 7.48 (m, 2H), 7.43 (m, 1H), 7.16 (m, 1H), 5.17 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 154.6, 149.8, 132.7, 129.9, 128.0, 127.9, 65.5. ^{19}F NMR (376 MHz, DMSO-d6) δ −135.67 (m, 2F), −146.95 (m, 2F)
VI	156–159 °C (EA) /yellow solid	^{1}H NMR (400 MHz, DMSO-d6) δ 7.75 (m, 2H), 7.43 (m, 3H), 5.94 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 154.2, 151.2, 131.1, 130.5, 128.8, 126.8, 64.3. ^{19}F NMR (376 MHz, DMSO-d6) δ −145.49 (m, 2F), −153.58 (t, J = 22.9 Hz, 1F), −162.22 (m, 2F).
VII	132–134 °C EA) /orange solid	^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 149.0, 70.3, 16.9.

		^{19}F NMR (376 MHz, $CDCl_3$) δ −56.27 (t, J = 21.9 Hz, 3F), −139.25 (m, 2F), −142.71 (m, 2F).
VIII	141–144 °C (EA) /dark orange solid	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 148.2, 71.4, 17.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −137.67 (m, 2F), −144.95 (m, 2F).
IX	135–138 °C (EA) /orange solid	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21(m, 1H), 7.90 (m, 2H), 7.53 (m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 149.4, 134.8, 130.3, 129.5, 128.6, 68.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −56.17 (dt, J = 64.8, 21.9 Hz, 3F), −138.80 (m, 2F), −142.88 (m, 2F).
X	149–151 °C (EA) /orange solid	^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 148.9, 70.1, 16.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −141.89 (m, 2F), −152.19 (t, J = 22.8 Hz, 1F), −163.40 (m, 2F)
XI	136–139 °C (EA) /orange solid	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.47 (m, 8H), 6.88 (tt, J = 9.7, 7.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 150.1, 135.6, 130.8, 129.2, 128.6, 68.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −137.32 (m, 2F), −144.92 (m, 2F).
XII	138–140 °C (EA) /brown solid	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23(m, 1H), 7.88 (m, 2H), 7.50 (m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 150.4, 135.9, 130.9, 128.7, 127.9, 68.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.79 (m, 2F), −151.3 (t, J = 22.8 Hz, 1F), −165.67 (m, 2F)

[1] EA (ethyl acetate). [2] NMR signals of fluorinated carbons are omitted from the ^{13}C NMR chemical shifts due to numerous ^{1}J, ^{2}J and long-range couplings with magnetically non-equivalent fluorine from perfluorinated benzene moiety.

4. Conclusions

Presented work, as one of the first, describes synthetic utilization of nitrogen triiodide for iodination and azo bond formation on a series of pyrazole derivatives. Overall twelve derivatives were synthesised and characterized by NMR spectroscopy. This novel method ushers the possibility of preparation for broader spectrum of iodinated organic compounds and azo compounds. Its main advantages compared to other conventional iodination methods are high conversions, green solvent, quick reaction time, easy laboratory setup without the requirement of heating.

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