Convenient and Improved Halogenation of 3,5-Diarylisoxazoles Using *N*-Halosuccinimides

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Abstract: The convenient C-4 halogenation of 3,5-diarylisoxazoles using *N*-halosuccinimides (NBS, NCS, or NIS) in acetic acid is described. A strong acid catalyst was required for efficient halogenation of some isoxazoles depending on the substituent on the 5-phenyl ring. Finally, the 4-iodoisoxazoles were found to undergo a novel proto-deiodination upon heating in the presence of H_2SO_4.

Key words: isoxazoles, halogenation, N-halosuccinimides, iodo cleavage, solvent effects

3,5-Diarylisoxazoles, which are readily prepared from chalcone derivatives, comprise a common and much studied class of substituted isoxazoles.[1] Most recently, these types of isoxazoles have been studied as potential estrogen receptor modulators,[2] as potential anti-cancer[3] and anti-microbial agents,[4] as liquid crystals,[5] and as linear dyes with application to light-harvesting systems.[6]

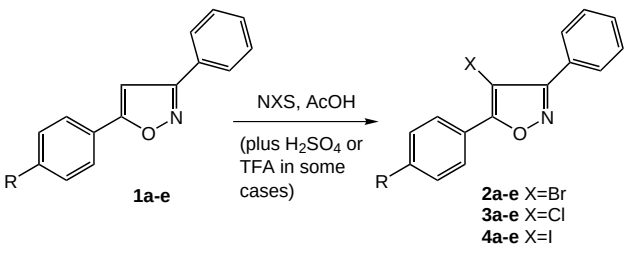
As halogen substitution can often lead to interesting changes in the physio-chemical and biological properties of aromatics,[7] including isoxazoles,[8] we are interested in 4-halo-3,5-diarylisoxazoles for the purpose of biological screening. Certain 4-haloisoxazoles (i.e. 4-bromo- and 4-iodoisoxazoles) are also of interest as they serve as intermediates to higher functionalized derivatives via metallation and/or transition metal-catalyzed chemistry.[2,9] Our search of the literature revealed that standard procedures for halogenation of aryl(or alkyl)-substituted isoxazoles at the C-4 position involve the use of strongly acidic conditions, oxidizing agents, or corrosive and reactive halogen. For example, such isoxazoles have typically been chlorinated with either Cl_2[1c] or HCl/H_2O_2,[10] have been brominated with Br_2 in the presence of either $AgSO_4/H_2SO_4$[11] or HNO_3,[12] and have been iodinated with I_2/HNO_3[12] and ICl.[13] In addition to the use of potentially hazardous reagents (particularly on a large scale), these chlorination and bromination conditions are occasionally limited by the formation of addition products subsequent to substitution.[10,14]

With the aim of developing improved procedures for the C-4 halogenation of 3,5-diarylisoxazoles, we have thus explored the use of N-halosuccinimides (i.e., NCS, NBS, NIS) as more convenient and milder sources of electrophilic halogen. As a result of their convenience in handling, as well as the improved regioselectivity that they sometimes offer, these reagents have received much attention recently for the nuclear halogenation of aromatics.[15–17] Regarding their use with non-activated isoxazoles, there is a single report in the literature[18] that details the bromination of some alkyl- and aryl-substituted isoxazoles with NBS in DMF. However, the conditions described therein proved to be unsatisfactory for halogenation of many of our diarylisoxazoles, apparently due to the effects of substituents on the phenyl rings. That same report, as well as a leading heterocyclic resource,[19] suggests that NIS is not suitable for the iodination of such isoxazoles, although during the course of this work Gershman and co-workers[2] have prepared a 4-iodo-3,5-diarylisoxazole using NIS in DMF.

As a result of our work in this area, we now wish to report convenient and improved procedures for the halogenation of a series of 5-aryl substituted 3,5-diarylisoxazoles with *N*-halosuccinimides, including NIS. In addition, we also describe the novel proto-deiodination of the 4-iodoisoxazoles, a process that was observed during some of our iodinations.

Results

The electron density, and thus reactivity, of C-4 of the isoxazole ring in 3,5-diarylisoxazoles is primarily affected by the electronic properties of substituents on the 5-phenyl ring (as opposed to the 3-phenyl ring).[20] We thus chose as substrates for halogenation a series of compounds (**1a**–**e**, Scheme 1) with varying substituents (i.e., R = H, OMe, Me, Br, or CF_3) at the para-position of the 5-phenyl ring. As these substituents range from strongly activating (OMe) to strongly deactivating (CF_3), these substrates were expected to vary somewhat in regards to their reactivity towards halogenation.



a R = H; **b** R = OMe; **c** R = Me; **d** R = Br; **e** R = CF_3

Scheme 1

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Bromination

In preliminary reactions, we found that isoxazoles **1a**–**c** could indeed be regioselectively brominated at the C-4 position in 3–6 h by heating with NBS in DMF at 130–140 °C. However, bromination of the deactivated bromo- or trifluoromethyl-substituted isoxazoles **1d**–**e** under these conditions proceeded quite sluggishly, with only minimal conversions observed after prolonged heating. As NBS has been activated by protonation with various acids,[16] we thus turned to refluxing acetic acid as solvent in place of DMF. With this single change, we found that bromination of the bromo-substituted isoxazole **1d** was complete in only 1.5 h (Table 1). Bromination of the trifluoromethyl-substituted isoxazole **1e**, on the other hand, remained sluggish and ultimately required excess NBS (2 equiv) and an extended reaction time (8 h) to go to completion.

Based on these results, the bromination of the more activated isoxazoles **1a**–**c** was repeated using acetic acid as solvent. With this change, we observed a noticeable decrease in the time required for complete bromination compared to reaction in DMF (i.e., from ca. 3–6 h to 1–2 h). Thus, the use of acetic acid appears to clearly accelerate the bromination of 3,5-diarylisoxazoles with NBS.

Chlorination

Based on the bromination results, the attempted chlorination of isoxazoles **1a**–**d** using *N*-chlorosuccinimide (NCS) (1.1 equiv) was initially performed in refluxing acetic acid. In general, chlorination under these conditions proceeded noticeably slower than did bromination with NBS, and only parent isoxazole **1a** and the activated OMe-substituted isoxazole **1b** could be efficiently chlorinated. In contrast, chlorination of the other isoxazoles (**1c**–**e**) was generally very slow and did not proceed to completion even with extended reaction times. While the diminished reactivity of **1d**–**e** towards NCS is likely due to the presence of the deactivating bromo and trifluoromethyl groups, the reason for the diminished reactivity of the methyl-substituted isoxazole **1c** is not readily apparent. It should be noted that by TLC no benzylic chlorination, or any other competing reaction, was detected in the case of **1c**.

For these less reactive isoxazoles, the use of a strong-acid catalyst was examined, and this was found to lead to a significant improvement in reaction outcome. Thus, with the addition of a catalytic amount of sulfuric acid (3–4 drops), the chlorination of isoxazoles **1c**–**d** with NCS (1.1–1.5 equiv) was complete in just a few hours (Table 1). However, the trifluoromethyl-substituted isoxazole **1e** again proved least reactive towards halogenation, still requiring an excess of NCS (3 equiv) and an extended reaction time (10 h) to be completely chlorinated.

Table 1 Results for Halogenation of Diarylisoxazoles **1a**–**e** with NXS in Refluxing HOAc

Product	X	R	Equiv NXS	Added Acid[a]	Reaction Time (h)	Yield[b] (%)	Mp (°C)
2a	Br	H	1.1		1.5	72	132–134[c]
2b	Br	OMe	”		1.5	52	141.5–142
2c	Br	Me	”		2.5	55	114–115
2d	Br	Br	”		1.5	86	118–119.5
2e	Br	CF_3	2		8	78	123.5–124
3a	Cl	H	1.1		1.5	80	84–85[d]
3b	Cl	OMe	”		5	37	109.5–110.5
3c	Cl	Me	1.5	H_2SO_4	5.5	59	108–109
3d	Cl	Br	1.1	H_2SO_4	2	88	110.5–111.5
3e	Cl	CF_3	3	H_2SO_4	10	70	122–122.5
4a	I	H	1.5		3	88	176.5–177.5[e]
4b	I	OMe	”	TFA	3[f]	97	158.5–159.5
4c	I	Me	1.8		3	76	90.5–91
4d	I	Br	2	TFA	3	59	151.5–152
4e	I	CF_3	4	TFA	10	84	170–170.5

[a] The addition of H_2SO_4 (3–4 drops) or trifluoroacetic acid (30 drops/5mL HOAc) was required for complete halogenation of certain substrates.
[b] Yield following recrystallization from EtOH or EtOH–H_2O.
[e] Lit. mp 171–172 °C.[12]
[c] Lit. mp 132.5–133.5 °C.[12]
[d] Lit. mp 84 °C.[10]
[f] Reaction was performed at r.t.

Iodination

There have been reports of both the success[2] and failure[18] of the iodination of a 3,5-diarylisoxazole with N-iodosuccinimide (NIS) in DMF. In our work, we found that the parent isoxazole **1a** and the methyl-substituted isoxazole **1c** were readily iodinated in just a few hours upon reaction with NIS in refluxing acetic acid. As a notable difference from the NBS and NCS reactions, a larger excess of NIS was required for complete iodination of each isoxazole due to substantial decomposition of NIS to elemental iodine during the reaction.

In contrast to the successful iodination of **1a** and **1c**, the reaction of isoxazoles **1b** and **1d**,**e** with NIS under the same conditions led to only partial conversion to iodinated product. Interestingly, in the case of methoxy-substituted isoxazole **1b**, we observed that prolonged heating actually resulted in nearly complete reconversion (deiodination) of product to starting material as judged by TLC. It thus appears that proto-deiodination is a competing process with

this more activated substrate. Indeed, such deiodination may have been the cause of the previously reported failure at iodination of a diarylisoxazole with NIS.[18] On the other hand, the incomplete iodination of bromo- and trifluoromethyl substituted isoxazoles **1d**,**e** appears to be simply due to the diminished reactivity of these substrates.

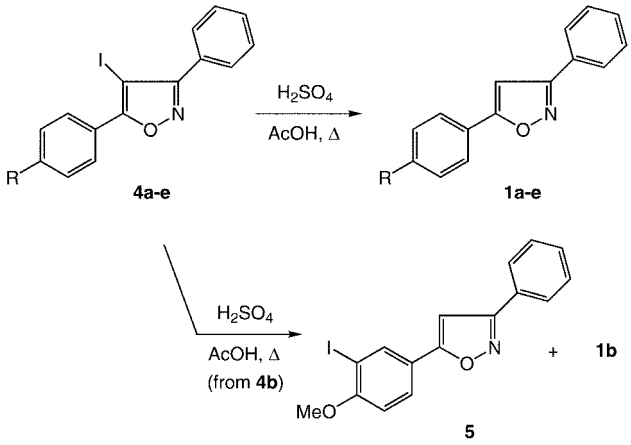
After much experimentation, we ultimately found that the methoxy-substituted isoxazole **1b** could be efficiently iodinated with NIS without deiodination by stirring at room temperature in a mixture of acetic and trifluoroacetic acid.[17] Similarly, deactivated isoxazoles **1d**,**e** were readily iodinated by refluxing with NIS in the same acid mixture, although the trifluoromethyl-substituted isoxazole required an even larger excess of NIS (4 equiv). In each of these cases, the trifluoroacetic acid apparently serves to activate the NIS by protonation,[17] but does not lead to subsequent deiodination.

As summarized in Table 1, the use of *N*-halosuccinimides (NCS, NBS, or NIS) gave the halogenated isoxazoles **2**–**4** in good to excellent yields. In all cases, halogenation was highly regioselective for C-4 of the isoxazole ring, with essentially clean conversion to a single, more lipophilic product typically observed by TLC. This includes when a strong acid was used for activation of the *N*-halosuccinimide, as well as when an activated phenyl ring was present. Once halogenation was complete, simple dilution of the reaction mixture with water (or aqueous thiosulfate to remove iodine in the case of iodination) gave the nearly pure product, which was collected and recrystallized from ethanol or ethanol–water. As 10–25% of product was often lost upon recrystallization, reported yields may not be optimized.

Each halogenated isoxazole prepared was characterized by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. The location of the halogen was confirmed by the absence of both the singlet for the C-4 proton in the ^{1}H NMR and the strong isoxazole C–H stretch at ca. 3100–3120 cm^{-1} in the IR, as well as by a distinct shift for C-4 in the ^{13}C NMR. Thus, while the signal for C-4 of the parent isoxazoles is found at ca. 96–100 ppm in the ^{13}C NMR,[20] this signal is found at ca. 102–106 ppm for the chloroisoxazoles, at ca. 88–92 ppm for the bromoisoxazoles, and at ca. 55–61 ppm for the iodoisoxazoles. Such a large upfield shift for the 4-iodoisoxazoles is consistent with that found with the analogous 4-iodopyrazoles.[21]

Deiodination

With iodoisoxazoles **4a**–**e** in hand, we further explored the acid induced deiodination of these compounds as previously observed in the synthesis of **4b**. While the iodo compounds proved stable to refluxing acetic acid, the addition of a few drops of sulfuric acid to the refluxing solution led to a slow, yet complete, deiodination back to the parent isoxazoles (Scheme 2). In the deiodination of **4b**, the iodide interestingly underwent partial migration to the activated phenyl ring to give a mixture of compound **5** and deiodinated parent **1b**. Pure **5** was isolated in 10% yield by recrystallization.



Scheme 2

The mechanism for deiodination apparently involves C-4 protonation, followed by attack of iodide by acetic acid to form iodine acetate[22,23] and regenerate the parent isoxazole. In the case of **4b**, iodine acetate apparently served as an iodinating agent[22] to give compound **5**. It is noteworthy that the 4-bromoisoxazoles were not debrominated under the same conditions.

This appears to be the first report of the protodeiodination of any iodoisoxazole, although it has been observed with other aromatic systems.[24] In some cases, as with benzene[25] and imidazole[26] derivatives, an easily removed halogen is used as a protecting group to block electrophilic attack at a more reactive position. The current finding suggests the same strategy (i.e., blocking the reactive C-4 position) may be possible with less substituted isoxazoles, although its application remains to be shown.

In conclusion, we have developed convenient and improved procedures for halogenation of 3,5-diarylisoxazoles with *N*-halosuccinimides (NBS, NCS, or NIS). Key to the success of many of these halogenations is the use of an acid catalyst for activation of the N-halosuccinimide, particularly for those isoxazoles containing deactivating substituents on the phenyl rings. Finally, the 4-iodoisoxazoles were found to undergo protodeiodination back to the parent isoxazoles upon heating in acetic acid/sulfuric acid.

Starting isoxazoles were prepared from the appropriate chalcone derivative via standard chemistry[27] and characterized by ^{13}C NMR as outlined in the literature.[20] *N*-Halosuccinimides were obtained from Aldrich Chemical Co. and used as received. All NMR spectra were recorded on a Varian Unity+300 instrument at 30 °C. Unless otherwise noted, DMSO-d_6 was used as NMR solvent, with the solvent peak serving as reference (2.49 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). IR spectra were obtained on a Perkin One instrument (KBr diffuse reflectance). Elemental analyses were obtained on a Perkin Elmer 2400 (Series II) analyzer.

Table 2 IR and NMR Spectral Data for 4-Haloisoxazoles **2**–**4**

Product[a]	IR (KBr) cm^{-1}	^1H NMR (DMSO-d_6) δ, *J* (Hz)	^{13}C NMR (DMSO-d_6) δ
2a	3056, 1613, 1589, 1570, 1446, 1114, 768, 707, 693, 517	7.58–7.66 (m, 6 H), 7.78–8.81 (m, 2 H), 8.01–8.04 (m, 2 H)	89.8, 125.9, 126.8, 127.2, 128.4, 129.0, 129.3, 130.5, 131.2, 161.9, 165.5
2b	3006, 2972, 2839, 1614, 1504, 1264, 1181, 1103, 1025, 831, 697, 568, 527	3.85 (s, 3 H), 7.16 (d, *J* = 9.0, 2 H), 7.57–7.59 (m, 3 H), 7.77–7.80 (m, 2 H), 7.98 (d, *J* = 9.0, 2 H)	55.4, 88.2, 114.7, 118.3, 127.3, 128.3, 128.4, 128.8, 130.4, 161.2, 161.7, 165.4
2c	3053, 2915, 2869, 1614, 1501, 1444, 1389, 1104, 991, 820, 696, 513	2.40 (s, 3 H), 7.43 (d, *J* = 8.0, 2 H), 7.58–7.60 (m, 3 H), 7.78–7.81 (m, 2 H), 7.93 (d, *J* = 8.1, 2 H)	21.0, 89.1, 123.2, 126.6, 127.2, 128.3, 128.9, 129.7, 130.4, 141.2, 161.7, 165.5
2d	3064, 1601, 1485, 1402, 1383, 1100, 1075, 833, 696, 508	7.57–7.61 (m, 3 H), 7.77–7.86 (m, 4 H), 7.97 (d, 2 H)	90.4, 124.8, 125.1, 127.0, 128.4, 128.7, 129.0, 130.6, 132.4, 162.0, 164.5
2e	3057, 1621, 1445, 1412, 1328, 1171, 1117, 1103, 1068, 844, 771, 708	7.58–7.61 (m, 3 H), 7.79–7.82 (m, 2 H), 8.00 (d, *J* = 8.4, 2 H), 8.25 (d, *J* = 8.3, 2 H)	91.5, 121.9, 125.5, 126.1, 126.2, 126.2, 126.3, 126.9, 127.6, 128.4, 128.9, 129.6, 130.6, 130.6, 131.0, 162.0, 163.9
3a	3059, 1616, 1571, 1493, 1448, 1399, 1127, 769, 707, 692	7.58–7.63 (m, 6 H), 7.82–7.85 (m, 2 H), 7.99–8.03 (m, 2 H)	104.1, 125.5, 126.3, 126.5, 128.0, 129.0, 129.3, 130.6, 131.2, 160.4, 163.8
3b	3057, 3009, 2972, 2840, 1614, 1505, 1444, 1393, 1305, 1259, 1108, 1026, 832, 698	3.85 (s, 3 H), 7.16 (d, *J* = 9.0, 2 H), 7.57–7.59 (m, 3 H), 7.80–7.83 (m, 2 H), 7.96 (d, *J* = 9.0, 2 H).	55.4, 102.5, 114.8, 117.9, 126.7, 128.0, 128.0, 129.0, 130.5, 160.2, 161.2, 163.8
3c	3068, 2916, 1615, 1503, 1445, 1392, 1116, 1007, 821, 770, 695	2.39 (s, 3 H), 7.42 (d, *J* = 7.8, 2 H), 7.57–7.60 (m, 3 H), 7.80–7.83 (m, 2 H), 7.90 (d, *J* = 8.0, 2 H)	21.0, 103.5, 122.8, 126.2, 126.6, 128.0, 129.0, 129.8, 130.6, 141.2, 160.3, 163.9
3d	3090, 3060, 1604, 1486, 1458, 1403, 1390, 1011, 831, 771, 719, 696, 485	7.57–7.61 (m, 3 H), 7.79–7.84 (m, 4 H), 7.94 (d, 2 H)	104.6, 124.6, 124.8, 126.4, 128.0, 128.2, 129.1, 130.7, 132.4, 160.4, 162.8
3e	3060, 1601, 1446, 1414, 1328, 1172, 1108, 845, 771, 708	7.59–7.61 (m, 3 H), 7.82–7.84 (m, 2 H), 7.99 (d, *J* = 8.3, 2 H), 8.22 (d, *J* = 8.2, 2 H)	105.8, 121.9, 125.5, 126.2, 126.2, 126.3, 126.3, 127.1, 128.0, 129.1, 130.5, 130.8, 131.0, 160.5, 162.3
4a	3053, 1610, 1583, 1564, 1486, 1445, 1389, 1107, 983, 765, 693	7.57–7.62 (m, 6 H), 7.73–7.76 (m, 2 H), 8.01–8.04 (m, 2 H)	59.5, 126.8, 127.5, 128.5, 128.8, 128.8, 129.1, 130.2, 131.0, 164.7, 168.5
4b	3060, 3004, 2977, 2943, 2837, 1611, 1500, 1258, 1181, 1094, 1023, 981, 831, 697	3.85 (s, 3 H), 7.16 (d, *J* = 9.0, 2 H), 7.56–7.58 (m, 3 H), 7.71–7.74 (m, 2 H), 7.98 (d, *J* = 9.0, 2 H)	55.4, 57.6, 114.5, 119.1, 128.6, 128.7, 128.7, 129.1, 130.1, 161.1, 164.6, 168.4
4c	3063, 2911, 1611, 1500, 1380, 1097, 982, 819, 695, 512	2.40 (s, 3 H), 7.42 (d, *J* = 8.1, 2 H), 7.56–7.58 (m, 3 H), 7.71–7.75 (m, 2 H), 7.92 (d, *J* = 8.1, 2 H)	21.0, 58.6, 124.0, 127.3, 128.5, 128.7, 128.7, 129.6, 130.1, 140.9, 164.6, 168.6
4d	3082, 3054, 1603, 1483, 1456, 1397, 1094, 983, 830, 770, 720, 695, 514	7.55–7.60 (m, 3 H), 7.71–7.75 (m, 2 H), 7.82 (d, *J* = 9.0, 2 H), 7.97 (d, *J* = 9.0, 2 H)	60.0, 124.5, 125.9, 128.3, 128.7, 129.3, 130.2, 132.1, 164.8, 167.4
4e	3063, 1571, 1408, 1330, 1167, 1127, 1098, 1068, 843, 771, 708, 697	7.57–7.60 (m, 3 H), 7.73–7.76 (m, 2 H), 7.99 (d, *J* = 8.4, 2 H), 8.25 (d, *J* = 8.3, 2 H)	61.3, 122.0, 125.6, 126.0, 126.0, 126.1, 126.1, 128.2, 128.3, 128.7, 128.8, 130.0, 130.3, 130.4, 130.6, 130.9, 164.9, 167.0

[a] Satisfactory microanalysis were obtained: C,±0.29; H,±0.19; N,±0.19.

4-Halo-3,5-diarylisoxazoles 2-4; General Procedure

A solution of the isoxazole **1a**–**e** (0.5–1.5 mmol) and the *N*-halosuccinimide (1.1 equiv of NBS or NCS, or 1.5 equiv of NIS) in HOAc (5 mL/mmol of isoxazole) was heated at gentle reflux (open condenser) with the reaction progress followed by TLC (EtOAc–hexanes). If halogenation was judged to no longer be proceeding, additional NXS was added in increments until starting material was consumed (total NXS and reaction times given in Table 1). With some substrates, halogenation remained sluggish with addition of excess NXS, and thus the reaction sequence was repeated using a strong acid catalyst. Once halogenation was complete, the solution was diluted with H_2O (or aqueous $Na_2S_2O_3$ solution in the case of iodination), and the resulting precipitate was collected, washed with water, and recrystallized from EtOH or EtOH–H_2O. Yields and analytical data are given in Table 1 and Table 2. As noted in Table 1, iodination of **1b** was performed at r.t. To minimize decomposition of NIS, all iodination reactions were protected from light by aluminum foil.

Deiodination of 4-Iodoisoxazoles 4; General Procedure

To the 4-iodoisoxazole (0.33 mmol) in HOAc (2 ml) was added 5–6 drops of concentrated H_2SO_4 and the mixture was heated at gentle reflux until TLC analysis showed deiodination to be complete (24–48 h). The solution was then diluted with H_2O and the resulting solid was collected, rinsed with H_2O, and air dried (yield: 80–90%). The structure of the product was confirmed by comparison of the ^1H NMR, IR, and TLC to that of authentic samples. With **4b**, a mixture of **1b** and **5** was obtained after 48 h, with **5** predominating. Slow recrystallization from EtOH–H_2O gave pure **5** as colorless needles in 10% yield.

5-(3-Iodo-4-methoxy)-3-phenylisoxazole (5)

Mp 143.5–144.5 °C.

IR: 3096, 3059, 2975, 2944, 1610, 1492, 1466, 1280, 1269, 757, 686 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.95 (s, 3 H), 6.73 (s, 1 H), 6.91 (d, *J* = 8.7 Hz, 1 H), 7.47–7.50 (m, 3 H), 7.80–7.87 (m, 3 H), 8.24 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR: δ = 56.7, 86.9, 97.9, 111.9, 121.3, 126.5, 127.2, 128.6, 129.1, 130.3, 136.0, 159.3, 162.6, 168.2.

Anal. Calcd for $C_{16}H_{12}INO_2$ (377.18): C, 50.95; H, 3.21; N, 3.71. Found: C, 51.07; 3.18; N, 3.60.

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