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Synthesis, Characterization, and Reactivity of an Ethynyl Benziodoxolone (EBX)−Acetonitrile Complex

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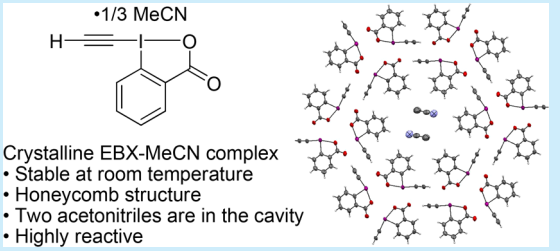
Supporting Information

ABSTRACT: The synthesis of a crystalline ethynyl-1,2-benziodoxol-3(1*H*)-one (EBX)−acetonitrile complex is described. EBX has been widely used as an active species for a variety of reactions; however, its high instability has so far prevented its isolation. The EBX−acetonitrile is self-assembled into a double-layered honeycomb structure through weak hypervalent iodine secondary interactions and hydrogen bonding. The *N*-ethynylation of a variety of sulfonamides using the EBX−acetonitrile complex as a substrate under mild conditions is also described.



The terminal alkyne is a very important and useful functional group not only in the organic synthetic field but also in other fields such as biochemistry and material science.[1] Thus, the development of ethynylating reagents that are applicable to the manufacturing of biological compounds and complex molecules under mild conditions, thereby expanding the application scope of this rich alkyne chemistry, is of high interest. In regular nucleophilic alkynylation reactions of carbonyls or imines[2] and cross-coupling reactions,[3] the reactivity of terminal alkynes is governed by the high acidity of the alkyne C(sp)−H bond. In contrast, umpolung, electrophilic alkynylation reactions involve C(sp)−X (X = Br, Cl, F, Pb(III), I(III)) bonds.[4] Especially, the highly electron-withdrawing nature[5] and hyper-leaving group ability of the λ^3-iodanyl group[6] of alkynyl hypervalent iodine compounds (X = I(III)) have been exploited in the electrophilic alkynylation.[7] The first alkynyl iodonium salt (**1**) was reported in 1965 (Figure 1).[8a] In 1988, a silyl protected ethynyl iodonium derivative (**2**) was synthesized by Stang,[8b] which was followed shortly after by the independent reports by Ochiai and Stang on unprotected ethynyl iodonium salts having different counteranions (BF_4 (**3**) and OTf (**4**)).[9a,b]

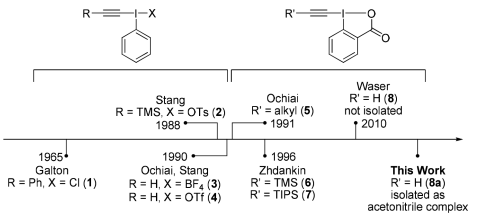


Figure 1. Alkynyl hypervalent iodine(III) compounds.

In the past decade, the chemistry of benziodoxol(on)e derivatives has attracted considerable interest because of their higher stability compared with their acyclic analogs.[7,10] Although the first cyclic hypervalent iodine was synthesized over 100 years ago, the history of alkynyl benziodoxolone (**5**−**8**, Figure 1) is comparatively short, probably because the internal carboxylate easily reacts with the alkynyl hypervalent iodine.[8c,d] In 1991, the first synthesis of alkynyl benziodoxolone (**5**) was achieved by Ochiai.[11a] In 1996, Zhdankin reported silyl-protected EBX derivatives (TMS-EBX (**6**) and TIPS-EBX (**7**)).[11b] In 2010, Waser reported the α-ethynylation of activated carbonyl derivatives using unprotected EBX (**8**) as crucial active species.[12a] EBX is generated in situ from TMS-EBX by using TBAF; however, it decomposes at around −20 °C in dichloromethane. Recently, EBX has been used as an active species for various reactions, including enantioselective ethynylation. Nevertheless, due to its instability, all attempts at its isolation have been unsuccessful.[12]

Coordination of additional ligands through hypervalent bonding and secondary bonding has been used to modify the stability and reactivity of hypervalent iodine.[7] For example, the physical and chemical properties of pseudocyclic hypervalent iodine compounds are significantly altered.[13] Furthermore, the intermolecular coordination of small molecules has been shown to stabilize the hypervalent iodine not only in the solid state but also in solution.[14] In this context, our group has recently focused on the stabilization of hypervalent iodine compounds through both internal and external coordination.[15] In view of the above-mentioned background, we hypothesized that deprotection of TMS-EBX with a mild base in a coordinating solvent would stabilize EBX, thereby enabling

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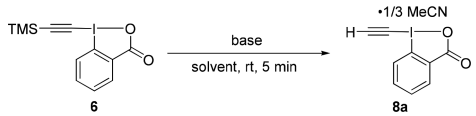
its synthesis and isolation. Herein, we report on the synthesis, isolation, characterization, and reactivity of the EBX–acetonitrile complex.

To prove our hypothesis, we commenced our study by using TBAF for the desilylation of TMS–EBX (**6**) in acetonitrile as a coordinating solvent (entry 1, Table 1). Unfortunately, EBX

Table 1. Study of Reaction Conditions for Desilylation[a]

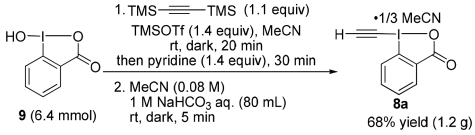


entry	solvent	base	yield (%) 8a	6
1[c]	MeCN	TBAF (1 equiv)	0	0
2[c]	MeCN	TBAF (1 equiv), 18C6 (1 equiv)	0	0
3	MeCN	$NaHCO_3$ (1 equiv)	36	19
4	MeCN	sat. $NaHCO_3$ aq. (5 mL)	21	31
5	EtCN	sat. $NaHCO_3$ aq. (5 mL)	31	3
6	EtOAc	sat. $NaHCO_3$ aq. (5 mL)	42	10
7	THF	sat. $NaHCO_3$ aq. (5 mL)	12	20
8	MeOH	sat. $NaHCO_3$ aq. (5 mL)	34	14
9	TFE	sat. $NaHCO_3$ aq. (5 mL)	41	1
10	HFIP	sat. $NaHCO_3$ aq. (5 mL)	16	38
11	$CHCl_3$	sat. $NaHCO_3$ aq. (5 mL)	0	53
12[d]	EtOAc	sat. $NaHCO_3$ aq. (5 mL)	14	0
13[d]	MeCN	sat. $NaHCO_3$ aq. (5 mL)	19	9
14[e]	MeCN	sat. $NaHCO_3$ aq. (5 mL)	20	33
15[f]	MeCN	sat. $NaHCO_3$ aq. (5 mL)	43	0
16[f]	MeCN	sat. Na_2CO_3 aq. (5 mL)	24	0
17[f]	MeCN	sat. K_2CO_3 aq. (5 mL)	23	3
18[f]	MeCN	sat. $NaHCO_3$ aq. (2.5 mL)	64	0
19[g]	MeCN	sat. $NaHCO_3$ aq. (5 mL)	69[b]	0
20[g]	MeCN	$NaHCO_3$ (1 equiv)	4	46
21[g]	MeCN	$NaHCO_3$ (100 equiv)	11	39

[a]Reaction conditions: **6** (0.025 mmol), base, solvent (0.5 mL), room temperature, air. Yields are determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b]Isolated yield. [c]Reaction carried out at −40 °C. [d]Reaction carried out for 30 min. [e]MeCN (0.25 mL). [f]MeCN (2.5 mL). [g]**6** (0.05 mmol), MeCN (5 mL). TBAF: tetrabutylammonium fluoride. 18C6: 18-Crown-6 ether. TFE: trifluoroethanol. HFIP: hexafluoro-2-propanol.

decomposed under these conditions affording 2-iodobenzoic acid as the sole product. Then, we used 18-crown-6 ether as a stabilizing agent; however, the same result was obtained (entry 2).[14a] In contrast, when using sodium bicarbonate instead of TBAF, a peak at 3.24 ppm attributable to C(sp)–H hydrogen was observed in the ^{1}H NMR spectrum, indicating the generation of EBX in a 36% NMR yield; however, unreacted TMS–EBX still remained in 19% yield (entry 3). Using an aqueous solution of sodium bicarbonate also gave EBX, albeit in low yield (entry 4). A screening of solvents revealed that the reaction progressed in polar solvents (entries 5–10), whereas nonpolar solvents such as chloroform gave no EBX (entry 11). Increasing the reaction time from 5 to 30 min resulted in decreased yields (entries 12 and 13), probably due to the instability of EBX in the presence of a base. Meanwhile, completion of the reaction was achieved upon decreasing the concentration to 0.01 M, affording EBX in 43% yield without any remaining TMS–EBX (entries 14 and 15). Regarding the base, saturated sodium bicarbonate aqueous solution gave the highest yield (entry 15 vs entries 16 and 17). Interestingly, when increasing the amount of starting **6** to 0.05 mmol, we obtained EBX in 69% yield with no TMS-EBX, and ^{1}H NMR analysis indicated that acetonitrile was contained in a 3:1 ratio (entry 19). In contrast, sodium bicarbonate gave lower yields on the 0.05 mmol scale (entries 20 and 21). With the optimized conditions for the deprotection of TMS-EBX in hand, we examined the synthesis of EBX from 1-hydroxy-1,2-benziodoxol-3-one (**9**). Scheme 1 summarizes the optimized conditions, which provided the desired EBX–acetonitrile complex (**8a**) in 68% yield (1.2 g) in two steps.

Scheme 1. Gram Scale Synthesis of EBX–Acetonitrile Complex



The synthesized EBX–acetonitrile complex (**8a**) is stable at room temperature, and no decomposition was observed when it was left standing under ambient conditions for 3 days. Surprisingly, this complex also remained stable for the same period in a chloroform solution, which contrasts with previous reports on EBX.[12,16] To elucidate the solid-state structure of the EBX–acetonitrile complex, a suitable single crystal of **8a** grown from acetonitrile was subjected to X-ray crystallographic analysis (CCDC 1886379; Figure 2).[17] The distorted three-coordinated T-shape geometry around the iodine displayed in Figure 2a is in good agreement with that of related compounds.[11] The complex adopts a distorted pentagonal planar geometry around the iodine atom due to the root-mean-square deviation of 0.094 Å (I1, C1, C2, O4, O3, and O1) from their least-squares plane and the sum of the iodine-centered bond angles of Σ°I1 = 360.6°. The nearly linear C1–I1···O4 angle (163.7°) and the relatively strong I1···O4 contact (2.819(3) Å) are indicative of the presence of hypervalent secondary interactions. Through these secondary bondings, EBX has a trimeric structure as reported previously for c-Hex-EBX and TBDPS-EBX (Figure 2a).[11a,d] Interestingly, one acetonitrile molecule seems to be weekly coordinated to the iodine center of an EBX from the other layer, with a N1···I2 distance of 3.473 Å, which is slightly shorter than the sum of the van der Waals radii (3.53 Å) (Figure 2a, Figure S2).[18,19] Note that TBDPS–EBX also contains an acetonitrile molecule in the crystal, albeit not coordinated to the iodine center.[11d] In contrast to other related alkynyl hypervalent iodine compounds, the trimer of EBX is linked with the adjacent three trimers via two hydrogen bondings, each of which involves an acidic acetylenic hydrogen atom and a carboxyl oxygen, forming a tetramer of EBX with a parallelogram structure (Figure 2a). The H1···O5 distance of 2.146 Å is shorter than their combined contact radii (2.72 Å),[19] and the C3–H1···O5 bond shows a nearly linear conformation with an angle of 166.06°. The ratio of isotropic displacement parameters U(C3)/U(C2) = 1.19) is close to 1, which supports the H1···O5 hydrogen bonding, since hydrogen bonding reduces the thermal vibrations of the engaged residues.[14a,20] Very interestingly, EBX is self-assembled into a double-layered honeycomb structure through hypervalent secondary bonding and hydrogen bonding (Figure 2b). Although the solid-state

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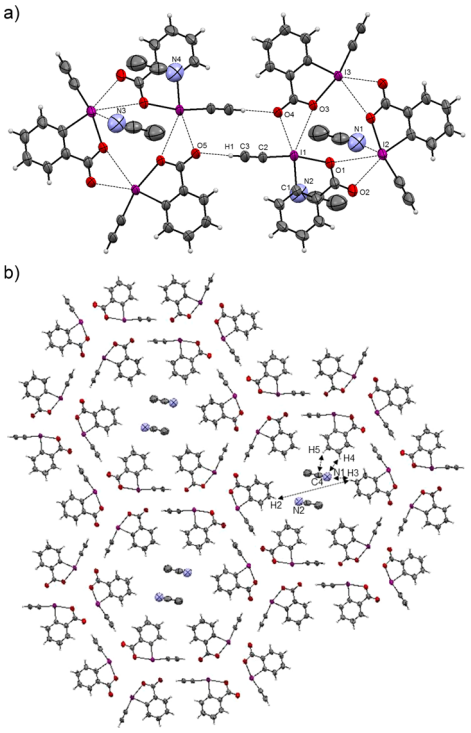


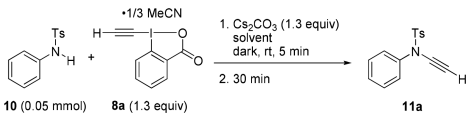
Figure 2. ORTEP drawing of **8a** (thermal ellipsoids set at 50% probability). (a) Top view of six EBXs. (b) Wider top view. Selected bond lengths [Å] and angles [deg]: I1−C1, 2.123(4); I1−C2, 2.043(3); I1−O1, 2.354(2); C2−C3, 1.170; I1···O3, 3.309(3); I1−O4, 2.819(3); C2−C3, 1.170(4); C3−H1, 0.930; H1···O5, 2.146; C1−I1−O1, 75.2(1); C1−I1−C2, 91.3(1); C2−I1−O1, 166.4(1); C1−I1···O4, 163.7; C1−I1···O3, 154.0; N1···I2, 3.473; H1···O5, 2.146; C3−H1···O5, 166.06; H2···H3, 10.019; N1···H3, 3.052; N1···H4, 2.931; C4···H5, 3.101.

structure of hypervalent iodine has been intensely studied, to the best of our knowledge, there is no precedent of such a honeycomb structure formed by hypervalent iodine compounds.[7,14] The linearity of the hydrogen bonding is key for the construction of the honeycomb structure by connecting the trimer of EBX, which works as a C_{3h}-symmetric molecular building block. Two acetonitrile molecules are included with opposite directions in the nanopores of the structure, which have diameters of ca. 10 Å (10.019 Å for H2···H3) probably due to the weak coordination of each acetonitrile to the iodine(III) center of the other layer (Figure 2b).[18] This structure provides an explanation for the EBX/acetonitrile ratio of 3:1 observed by ^{1}H NMR spectroscopy. Finally, no interaction between acetonitrile and the hydrogen atoms of the benzene ring is observed, since the distances N···H and C···H (N1···H3, 3.052 Å; N1···H4, 2.931 Å; C4···H5, 3.101 Å) are longer than the sum of the corresponding van der Waals radii (2.75 Å for N and H; 2.9 Å for C and H).[18,19]

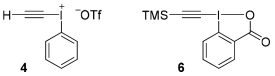
To gain more insight into the stability of the EBX−acetonitrile complex, **8a** was subjected to thermogravimetric/differential thermal analysis (TG−DTA)(Figure S1). The results showed that the included acetonitrile molecule was not released from the nanopores at the boiling point of acetonitrile (82 °C), but **8a** was decomposed above 100 °C to give the tar. After decomposition, the weight of **8a** decreased by ca. 50%, and the corresponding ^{1}H NMR spectrum showed that the decomposition product contains 2-iodobenzoic acid. These observations suggest that the presence of guest acetonitrile molecules is essential to preserve the honeycomb structure of EBX. Then, we tried to replace the acetonitrile molecule with other solvents by evaporation with various solvents. The corresponding ^{1}H NMR spectroscopic analysis revealed that related EBX−ethyl acetate (**8b**) and EBX−chloroform (**8c**) complexes were obtained in an EBX/solvent ratio of 6:1 in both cases. This result indicates that one ethyl acetate or chloroform molecule was captured in the honeycomb structure. Importantly, the stability of these complexes (**8b** and **8c**) is similar to that of **8a** not only in the solid state but also in chloroform solution, indicating that, in the absence of a base, coordination of acetonitrile is not required for the stability of EBX in chloroform.

Next, we examined the reactivity of the synthesized EBX−acetonitrile complex (**8a**). Ynamides are unique and synthetically valuable building blocks for organic synthesis and other fields.[21] *N*-Ethynylation with highly reactive alkynyliodonium salts, which was first reported by Stang,[9c] has been broadly used for the synthesis of ynamides. In contrast, *N*-alkynylation using EBX derivatives is highly limited. Cossy reported the *N*-ethynylation of sulfonamide to construct the tetrahydropyrazine framework using a strong base (NaH); however, the substrate scope was limited to primary sulfonamides.[12b] Therefore, we decided to explore the *N*-ethynylation using the EBX−acetonitrile complex (**8a**). Table 2 summarizes the results obtained. Using the optimized reaction conditions (Method A), ynamide **11a** was obtained in 90% yield (entry 7, Table 2). Note that ethynyl iodonium **4** and TMS-EBX **6** gave a lower yield of product under the present conditions (entries 8 and 9).

Table 2. Study of Reaction Conditions for *N*-Ethynylation with EBX−Acetonitrile Complex[a]



entry	solvent	Yield (%)
1	DMF	42
2	MeCN	63
3	EtOAc	66
4	MeOH	80[b]
5	IPA	80
6	1-propanol	87[b]
7[c]	1-propanol	90[b], 88[b,f]
8[c,d]	1-propanol	58
9[c,e]	1-propanol	64



[a]Reaction conditions: **10** (0.05 mmol), Cs_2CO_3 (0.065 mmol), solvent (1 mL), room temperature, 5 min, dark, argon. Then, **8a** (0.065 mmol), room temperature, 30 min, dark, argon. Yields are determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b]Isolated yield. [c]Cs_2CO_3 (1.2 equiv). [d]**4** was used instead of **8a**. [e]**6** was used instead of **8a**. [f]1 mmol scale reaction.

Then, we examined the scope and limitation of various sulfonamides (Scheme 2). Under the optimized conditions (Method A), methanesulfonamide and 4-nitrobenzenesulfonamide were transformed into the corresponding products **11b** and **11c** in 84% and 60% yields, respectively. In contrast,

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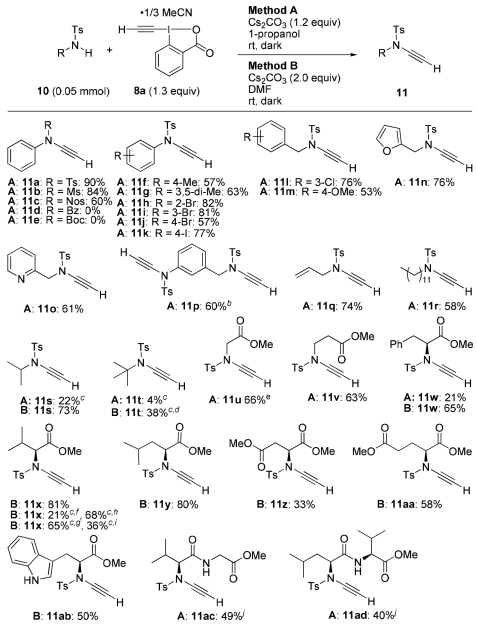
Scheme 2. Scope of the *N*-Ethynylation with EBX-Acetonitrile Complex[a]



[a]Reaction conditions: Method A: **10** (0.05 mmol), Cs_2CO_3 (0.06 mmol), 1-propanol (1 mL), room temperature, 5 min, dark, argon. Then, **8a** (0.065 mmol), room temperature, 30 min, dark, argon. Method B: **10** (0.05 mmol), Cs_2CO_3 (0.1 mmol), DMF (1 mL), room temperature, 5 min, dark, argon. Then, **8a** (0.065 mmol), room temperature, 30 min, dark, argon. Isolated yields. [b]Cs_2CO_3 (0.12 mmol) and **8a** (0.13 mmol) were used. [c]Yields are determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [d]**11t** was not isolated because it is labile. [e]MeOH was used instead of 1-propanol. [f]**4** was used instead of **8a**. **10x** was recovered in 53% yield. [g]**6** was used instead of **8a**. **10x** was recovered in 12% yield. [h]**4** (1.3 equiv), Cs_2CO_3 (1.3 equiv), DMF/DCM, rt, 3 h. **10x** was recovered in 28% yield. [i]**6** (1 equiv), NaH (1equiv), DMF, rt, 2 h. **10x** was recovered in 34% yield. [j]MeCN (1 mL) was used instead of 1-propanol (1 mL), 90 min.

amide and carbamate were recovered unchanged, as reported previously for TMS–EBX (**11d**, **11e**).[12b] Meanwhile, the reactions of methyl-, bromo-, and iodo-substituted *N*-tosylaniline, benzylamine, diamide, and primary aliphatic amine derivatives were ethynylated in good yields (**11f**–**11r**). In contrast, the sterically demanding amine derivatives gave the corresponding products in low yields (**11s**, **11t**). Since the *N*-alkynylation of amino acid derivatives with alkynyl hypervalent iodine to give the corresponding amino acid derived ynamide has been rarely reported,[9d] we applied our reaction conditions to amino acid derived tosylamides. Thus, glycine and *β*-alanine derivatives gave the corresponding ynamide products **11u** and **11v** in good yields, respectively; however, the phenylalanine derivative **10w** afforded the desired product **11w** only in 21% yield. Thus, we optimized further the reaction conditions with phenylalanine derivative **10w**. Using dimethylformamide (DMF) as a solvent and 2 equiv of Cs_2CO_3 (Method B), **11w** was obtained in an improved 65% yield. This condition also provided higher yields of the sterically demanding amine-derived ynamides (**11s**, 73%; **11t**, 38%). Then, Method B was used to investigate various *N*-tosylamino acid derivatives. Valine, leucine, aspartic acid, glutamic acid, and tryptophan derivatives gave the corresponding products in moderate to high yields (**11x**–**11ab**). Note that the valine derivative gave ynamide **11x** in a lower yield when using ethynyl iodonium salt **4** and TMS-EBX **6** as substrates under our and previously reported conditions.[9d,12b] Furthermore, dipeptides were selectively ethynylated at the sulfonamide in moderate yields (**11ac**, **11ad**).[12b] It is worth noting that these amino acid and peptide derived ynamides are new products. These results demonstrate the useful reactivity of **8a**, which allowed the performance of the ethynylation reaction under mild conditions using a simple procedure.

In conclusion, we have presented the synthesis, characterization, and reactivity of a crystalline ethynyl-1,2-benziodoxol-3(1*H*)-one (EBX)–acetonitrile complex (**8a**). EBX–acetonitrile **8a** is self-assembled through weak interactions into a rigid double-layered honeycomb structure, containing two acetonitrile molecules in the cavity. These results show the potential of cyclic hypervalent iodine in the crystal engineering field. Furthermore, using EBX–acetonitrile **8a**, the *N*-ethynylation of sulfonamides, including amino acid and peptide derivatives, to produce ynamides could be performed under mild and simple reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00005.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1886379 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(16) The ^{1}H NMR experiment in $CDCl_3$ at room temperature showed that EBX was decomposed in the presence of TBAF (1 equiv) within 5 min.
(17) Crystallographic data for **8a**: $C_{29}H_{18}I_3NO_6$, M_r = 857.14, T = 193 K, triclinic, space group $\bar{P}1$, a = 10.9814(2) Å, b = 11.2640(2) Å, c = 12.5836(3) Å, β = 98.3154(17)°, V = 1429.78(5) Å^3, Z = 2, μ (Mo Kα) = 3.32 mm^{-1}. 6499 reflections were collected. R = 0.030, wR = 0.071, GOF = 1.045.
(18) Acetonitrile is disordered probably because the acetonitrile can coordinate to the other iodine(III) center on another layer. Thus, bond distances and angles from acetonitrile are not accurate.
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