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Oxidative-substitution reactions of electron-rich aromatic compounds with BF_3-activated iodonium ylides

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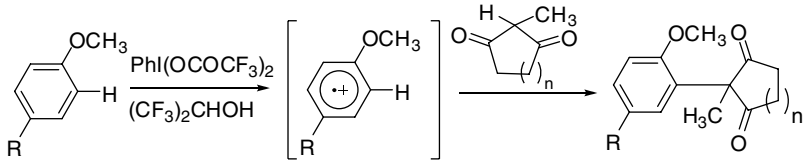
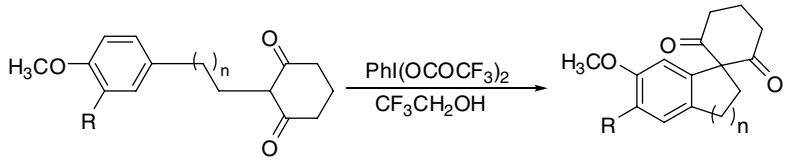
Abstract—The treatment of electron-rich aromatic substrates with phenyliodonium bis(carbonyl)methylides in the presence of $Et_2O{\cdot}BF_3$ leads to bis(carbonyl)alkylation of the aromatic nucleus.

The use of phenyliodine(III) bis(trifluoroacetate), (PIFA), in $(CF_3)_2CHOH$ or CF_3CH_2OH for the functionalization of *para*-substituted phenol ethers with nucleophilic reagents; and evidence that such reactions are initiated by SET-oxidation of the phenol ethers with PIFA and proceed through arene cation-radical intermediates have been reported by Kita and coworkers.[1–5] Similar functionalizations of naphthalene, polymethylbenzenes, and heterocyclic substrates via the action of BF_3-activated PIFA in CH_2Cl_2 have also been described and are thought to occur by an analogous mechanism.[1,6] Of interest here is the finding that 2-acetylbutyrolactone and cyclic β-diketones (monoalkylated at C-2) are viable nucleophiles for PIFA-induced inter- and intramolecular bis(carbonyl)-alkylations of the phenol ether nucleus, examples of which are shown in Scheme 1.[2,5] However, the *p*-$MeOC_6H_4CH_2CH_2$– derivatives of dimethyl malonate, methyl acetoacetate, and acetylacetone did not give cyclic products upon treatment with PIFA,[5] and whether acyclic β-dicarbonyl compounds undergo intermolecular reactions of this type has not been reported.

It has recently been shown that phenyliodine(III) sulfonate reagents **1** can also participate in oxidative aromatic substitution reactions.[7] In particular, the



n = 1 (R = OMe, Pr^i); n = 2 (R = OMe)



n = 1(R = H, OMe); n = 2 (R = OMe)

Scheme 1.

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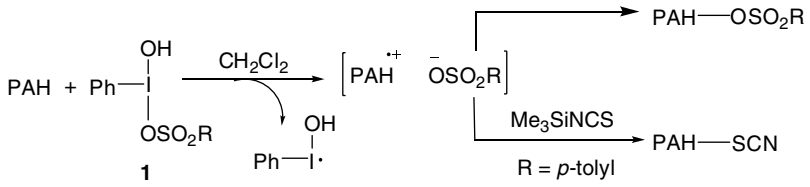


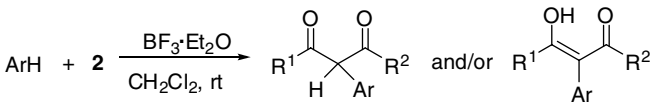
Scheme 2.

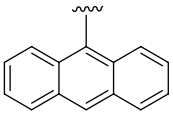
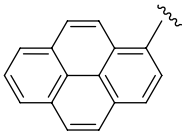
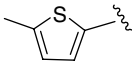
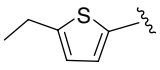
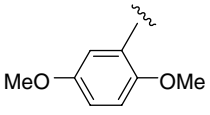
treatment of polycyclic aromatic hydrocarbons (PAH) with **1** in CH_2Cl_2 leads directly and regioselectively to PAH-sulfonate esters, and, when Me_3SiNCS is available, to PAH-thiocyanates (Scheme 2). In view of the reports that PIFA oxidations of polycyclic aromatic hydrocarbons in trifluoroacetic acid lead to ESR-observable cation-radicals;[8] and that phenyliodine(III) sulfonates (R = *p*-tolyl, 2-naphthyl, and 10-camphoryl) appear to be stronger oxidants than MnO_4^- and $Cr_2O_7^{2-}$,[9] the formation of PAH cation-radical intermediates in these reactions seems likely.

In connection with the foregoing study, we explored the possibility that phenyliodine(III) ylides[10–12] might undergo similar reactions with polycyclic aromatic hydrocarbons. We now report that the phenyliodonium β-dicarbonyl enolates **2** can be utilized with $Et_2O{\cdot}BF_3$ in CH_2Cl_2 for the installation of unsubstituted acyclic β-dicarbonyl groups into electron-rich aromatic substrates. This mode of reactivity was demonstrated with pyrene, anthracene, 2-alkylthiophenes, and 1,4-dimethoxybenzene.

In one experiment, $Et_2O{\cdot}BF_3$ (0.38 mL, 3.0 mmol) was added to a stirred solution of pyrene (0.203 g, 1.00 mmol) and ylide **2a** (0.503 g, 1.51 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was allowed to stir for 27 h at room temperature. After an aqueous workup

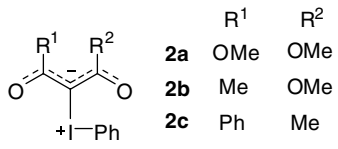
Table 1. Yields of chromatographically isolated products from the reactions of anthracene, pyrene, 2-alkylthiophenes, and 1,4-dimethoxybenzene with iodonium enolates **2a–c**



Ar	Entry[a,b]	R^1	R^2	Time (h)	Isolated yield (%)
	1	OMe	OMe	8.5	28 (37)
	2	Me	OMe	5	34 (43)
	3	Ph	Me	8	34 (45)
	4	OMe	OMe	27	38 (45)
	5	Me	OMe	4	32 (39)
	6	Ph	Me	7	34 (48)
	7	OMe	OMe	24	30
	8	Me	OMe	8	29
	9	Ph	Me	4	20
	10	OMe	OMe	24	29
	11	Me	OMe	24	39
	12	Ph	Me	24	15
	13	Me	OMe	1	32

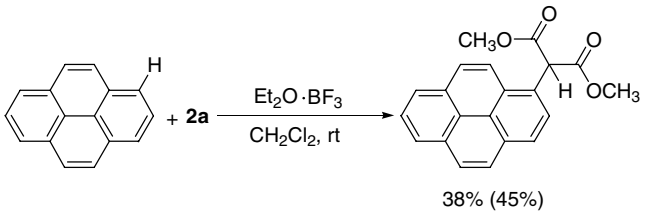
[a] With one exception (entry 13), the reactions were conducted with 1.00–1.07 mmol of ArH, 1.5 mmol of **2**, and 3.0 mmol of $Et_2O{\cdot}BF_3$ in 10 mL of CH_2Cl_2. In the case of entry 13, all quantities were halved. As a precautionary measure against air and light, the reaction vessels were equipped with a nitrogen-filled balloon and wrapped with aluminium foil. The reaction mixtures were stirred magnetically for the indicated (approximate) time periods prior to an aqueous workup. The yields in parentheses are corrected for the recovered starting material.

[b] Structural assignments are based on NMR ($CDCl_3$; ^1H and ^{13}C), FTIR (neat oils or solid films), and combustion (C,H) or HRMS-ESI (molecular weight) analysis. The molecular structures of two of the anthracene products (entries 2 and 3) were established unequivocally by single crystal X-ray analysis.



	R^1	R^2
2a	OMe	OMe
2b	Me	OMe
2c	Ph	Me

[$NaHCO_3$(aq); H_2O; $MgSO_4$] and solvent removal, a red oil was obtained. Column chromatography of the oil on silica gel with 20–50% $CHCl_3$/hexanes gave dimethyl 2-(pyren-1-yl)malonate as a pale-yellow solid: yield, 0.128 g (38%); mp 118–120 °C (recrystallized from MeOH); ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 6H), 5.78 (s, 1H), 8.01–8.26 (m, 9H); ^{13}C NMR ($CDCl_3$) δ: 53.25, 54.54, 122.36, 124.89, 125.23, 125.58, 125.91, 126.34, 126.52, 127.21, 127.57, 128.12, 128.81, 129.45, 130.76, 131.47, 131.57, 169.27; FTIR (solid film, cm^{-1}) 1750, 1736; Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.91; H, 4.99. Based on recovered pyrene (0.032 g, 0.16 mmol), the corrected yield of the product is 45%; Eq. 1.

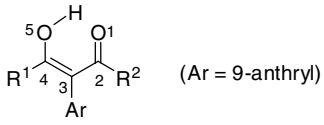


(1)

A similar treatment of various substrate–ylide combinations with BF_3-etherate in dichloromethane, followed by chromatography of the crude product mixtures on silica gel (usually with EtOAc/hexanes) gave moderate isolated yields of the aryl-substituted β-dicarbonyl compounds shown in Table 1.

Based on ^{1}H (300 MHz) and ^{13}C NMR analysis, the malonate derivatives in Table 1 appear to exist entirely as the keto tautomers, while the acetoacetate and benzoylacetone analogs reside predominately in their enol forms (i.e., except for entry 13), at least in $CDCl_3$. Spectral data for the 5-methyl-2-thienyl series (entries 7–9) serve to illustrate this point. For example, the NMR spectra of the malonate analog feature an α-hydrogen singlet at δ 4.86 and a typical saturated ester carbonyl peak at δ 168.06; and show no evidence for the enol tautomer. The benzoylacetone analog, on the other hand, is almost completely enolic. This is indicated by the presence of an enolic –OH singlet at δ 17.55 (and a very weak α-hydrogen singlet at δ 5.83) in the proton spectrum, and one vinylic (δ 106.85) and two carbonyl peaks (δ 184.15 and 198.52) in the carbon spectrum. The carbonyl chemical shifts are located upfield relative to those of acetophenone (δ 198.4) and acetone (δ 207.1) in $CDCl_3$ (this work), due to conjugation in the enol substructure, and are presumably weighted average chemical shifts for the two rapidly interconverting enol forms shown in Eq. 2. This phenomenon has been documented for β-dicarbonyl enols,[13] and such average ^{13}C-chemical shifts have been utilized for the estimates of enol–enol equilibrium constants.[14] The ^{1}H spectrum of the acetoacetate analog exhibits both enolic (δ 13.22) and α-hydrogen (δ 4.89) singlets and is consistent with a 6:1 enol/keto mixture. The ^{13}C spectrum shows a vinylic peak at δ 96.97 and four resonances in the carbonyl region; one pair of relatively weak intensity at δ 168.60 and 200.62 corresponding to the keto form,

Table 2. Selected bond distances of the 9-anthryl derivatives of methyl acetoacetate and benzoylacetone



	Bond distance (Å)			
R^1, R^2	C_2–O_1	C_4–O_5	C_2–C_3	C_3–C_4
Me, OMe	1.245 (3)	1.327 (3)	1.454 (3)	1.357 (3)
Ph, Me	1.2535 (17)	1.3282 (15)	1.444 (2)	1.3762 (19)

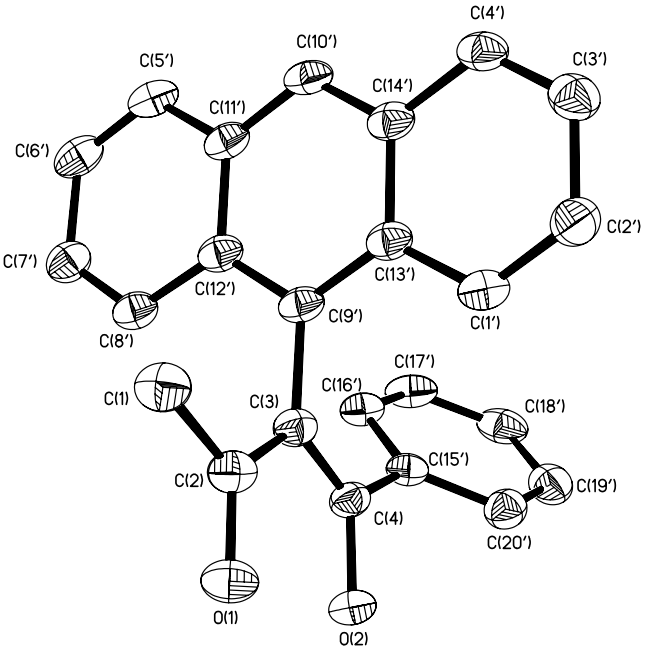
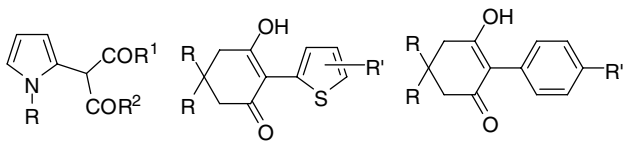


Figure 1. Thermal ellipsoid projection of (*Z*)-3-(anthracen-9-yl)-4-hydroxy-4-phenyl-3-buten-2-one.



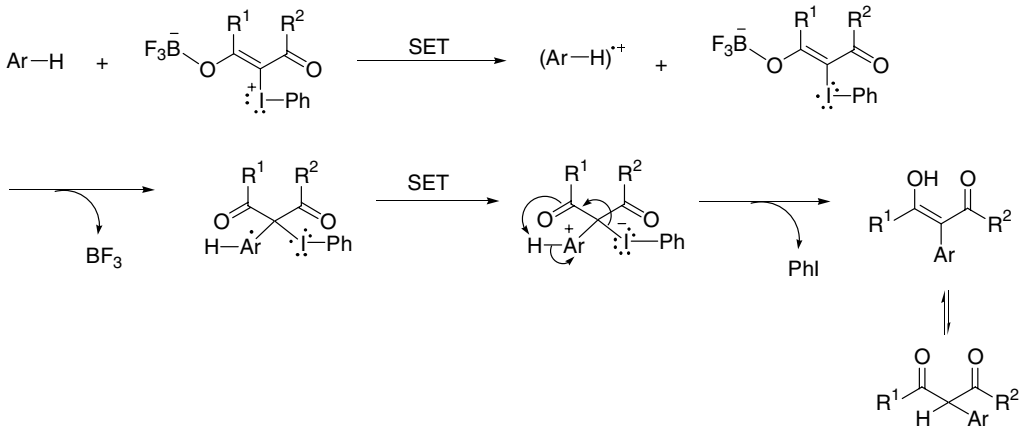
3 **4** **5**

R	R^1	R^2
H	MeO	MeO
Me	MeO	MeO
H	Me	MeO
Me	Me	MeO

R	R'
H	H
Me	H
Me	4-Me
Me	5-Me

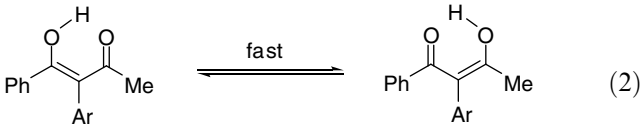
R	R'
H	H
Me	H
Me	OMe

Figure 2.



Scheme 3.

and another pair at δ 173.07 and 177.04 assigned to two rapidly-interconverting enol tautomers.



(Ar = 4-methyl-2-thienyl) (2)

That the 9-anthryl derivatives of methyl acetoacetate and benzoylacetone are also enolic in the solid state has been confirmed by single crystal X-ray analysis.[15] Selected bond distances for these compounds are given in Table 2, and are consistent with the indicated enolic forms. The molecular structure of the benzoylacetone analog is shown in Figure 1.

The ability of phenyliodonium enolates to behave as carbene-transfer agents, either in a formal sense or via carbene/carbenoid intermediates, is well known. Such reactions occur under thermal or photochemical conditions, or in the presence of transition metal catalysts, and follow dimerization, transylidation, cyclopropanation, or CH-insertion pathways.[11,12,16–21] Recent examples of CH-insertions include $Rh_2(OAc)_4$-catalyzed conversions of pyrroles, thiophenes, benzene, and anisole to the substituted β-dicarbonyl compounds **3**–**5** with the corresponding phenyliodonium enolates (Fig. 2).[22,23] Although the products of these reactions are of the same type as those shown in Table 1, they are presumably generated via carbene or carbenoid intermediates. We suggest that the BF_3-promoted reactions of **2** with electron-rich aromatics proceed by the arene cation-radical mechanism outlined in Scheme 3, and are mechanistically related to PIFA oxidations of *para*-substituted phenol ethers. This mechanism is based on the assumption that the BF_3-complexed iodonium enolates are stronger oxidants than the free ylides.

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