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Solvent directed electrophilic iodination and phenylselenenylation of activated alkyl aryl ketones

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Abstract—A mixture of molecular iodine and phenyliodine(III) bis(trifluoroacetate) (BTI) in CH_3CN (or CH_3OH) iodinates the aromatic ring of some activated alkyl aryl ketones. A different outcome results if PhSeSePh is used instead of I_2 in the presence of BTI. In CH_3CN the aromatic phenylselenenylation is still observed while in CH_3OH the formation of α-phenylseleno ketones occurs followed by the conversion of these intermediates into the corresponding α,α-dimethoxycarbonyl compounds, in moderate to good yields.

The ability of iodine(III) species to oxidise in situ a chalcogenate-type derivative such as diphenyl diselenide, or molecular iodine, has been extensively demonstrated and applied to the preparation of several oxyselenenylated products or iodohydrins respectively, starting from simple alkenes.[1,2] All these reactions proceed in a Markovnikov fashion. Additionally, good results have been reported by other groups in the field of heteroaromatic electrophilic substitution, for example, hypervalent and molecular iodine, in CCl_4, gave good yields in the iodination of monosubstituted thiophenes.[3] On the other hand the electrophilic thienylselenenylation of thiophene and furan derivatives was promoted by activation of 2,2′-dithienyldiselenide with $PhI(OCOCH_3)_2$.[4]

A very recent contribution showed the ability of Selectfluor™ F-TEDA-BF_4, typically used as a potent electrophilic fluorinating agent, to oxidise elemental iodine in different solvents. This reactive species is capable of selectively introducing an iodine atom at the α-carbonyl position of various alkyl aryl ketones in methanol solvent. When a CH_3CN solution of the reactive mixture is employed, electrophilic aromatic substitution occurred.[5]

These interesting results prompted us to extend our previous observations,[1,2] to the functionalisation of enolisable carbonyl derivatives. In order to reach this goal we have employed separately iodine and PhSeSePh, both activated in situ using the efficient and commercially available phenyliodine(III) bis(trifluoroacetate) (BTI), **1**. The first experiment was performed using I_2 in a solution of methanol in the presence of 4′-methoxyacetophenone at room temperature. BTI was added as the last reagent, and after a few minutes complete decolouration of the red brown solution was observed. By GC–EIMS analysis two peaks with the same $M^+ = 276$ appeared in the spectrum in a 95:5 ratio. The major product showed the fragment $m/z = 261$, probably derived from M^+ having lost a CH_3 group to give a stable benzoyl cation. This species contained one iodine atom linked to the aromatic ring. Moreover a CH_3CO fragment ($m/z = 43$), as base peak, was also detected. In contrast the less abundant compound did not contain this last fragment but showed an intense peak at $m/z = 135$, due to a stable benzoyl cation with no iodine atom bonded to its aromatic ring. After comparison with an authentic sample, we found that this last spectrum was due to a small amount of α-iodocarbonyl derivative present in the reaction mixture. The same experiment was repeated using CH_3CN as solvent and a single product derived from the regioselective aromatic iodination of 4′-methoxyacetophenone **2b**,[5] was detected in the reaction mixture. In all the experiments run in methanol and collected in Scheme 1, incomplete selectivity was observed. On the other hand, in acetonitrile, aromatic electrophilic substitution was the sole reaction observed. As shown in Scheme 1 the reactivity of the starting material seems to be associated with the electron density present in the

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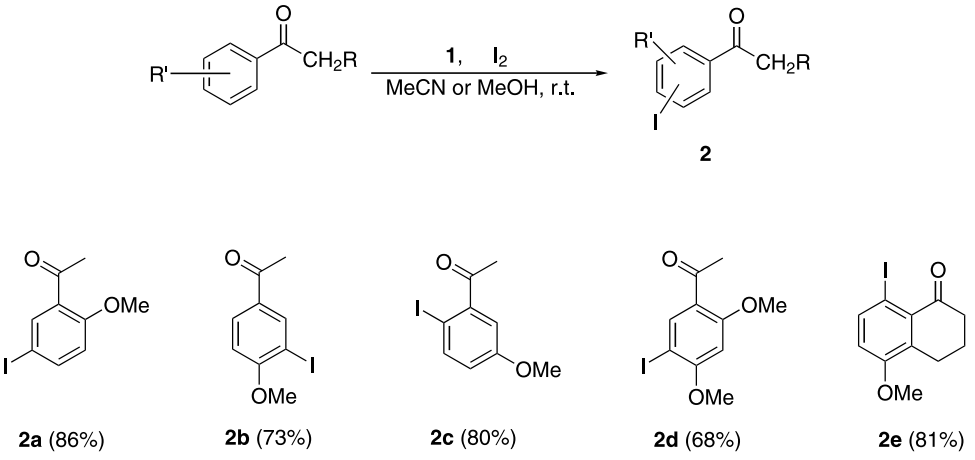


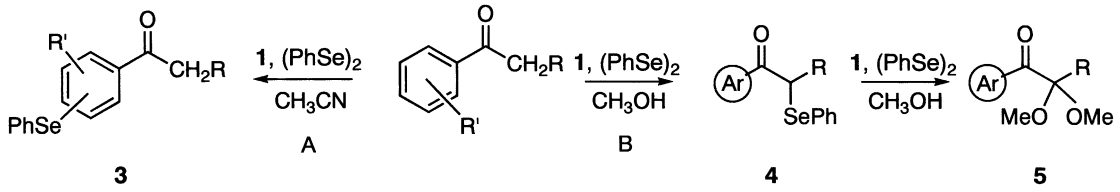
Scheme 1. Electrophilic aromatic iodination of alkyl aryl ketones.

the aromatic rings. Thus, the *p*-positions were exclusively iodinated to give **2a**,[5] **2c**[6] and **2e**, whereas *o*-iodination only occurred when the *p*-position was blocked with the acetyl substituent and thus **2b**[5] was formed. Position 5′ of 2′,4′-dimethoxyacetophenone is definitively the more activated and **2d**[5] is produced.[7]

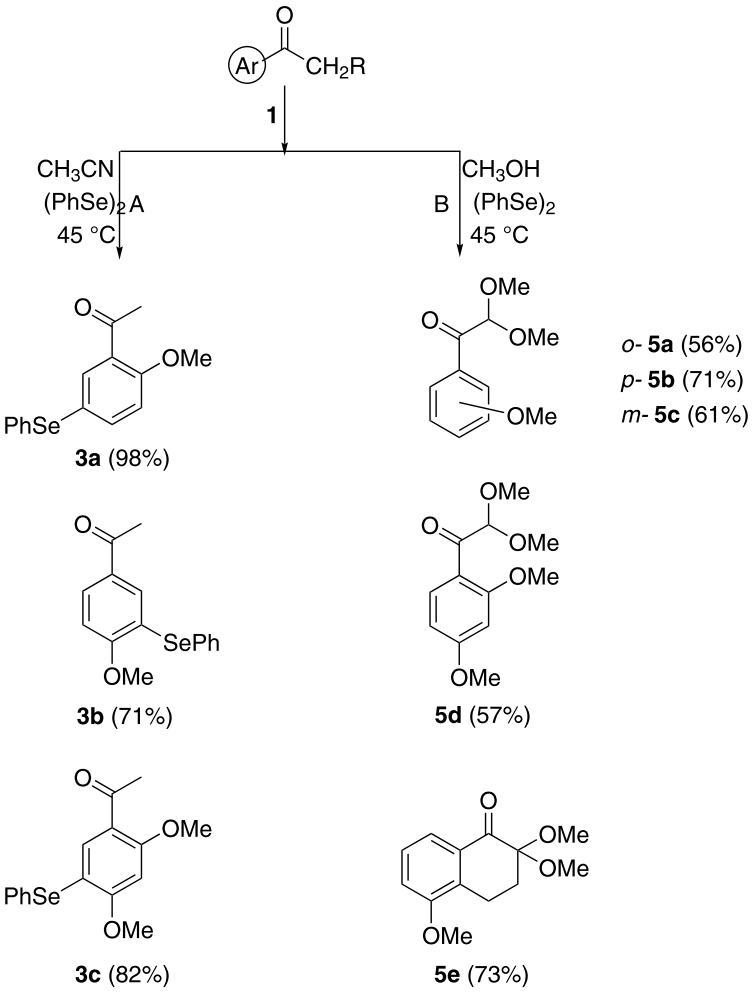
Our results seem to be partially in contrast with those obtained on similar exposure of methoxyacetophenones to Selectfluor™ and iodine[5] so perhaps the reactivity of the electrophilic iodine also depends on the oxidant species being chosen for its generation. Nevertheless, we have observed a small solvent effect probably due to a difference in enol content which is absent in CH_3CN where the only nucleophile is the aromatic ring, but is present in trace amounts in MeOH that favours an enol-derived pathway. This difference in enol content is enhanced when the BTI/PhSeSePh system is allowed to react with the same starting materials selected above for the iodination reactions. As depicted on the left of Schemes 2 and 3, the electrophilic PhSe species generated in situ by the interaction of BTI and diphenyldiselenide seems to be less reactive, but is much more selective in comparison with the corresponding BTI/I_2 system.

In acetonitrile at 45°C, the selenium moiety is able to functionalise selectively the aromatic rings even if in the presence of more activated methoxyacetophenones. Thus both 2′- and 4′-methoxyacetophenones underwent the phenylselenenylation reaction at the 5′ and 3′ positions to give compounds **3a** and **3b**, respectively. Also, 2′,4′-dimethoxyacetophenone was phenylselenenylated at the 5′ position to give **3c**. In contrast, no reaction occurred with either 3′-methoxyacetophenone or 5′-methoxytetralone. Clearly these rings are nucleophilic enough to react with iodine (see products **2c** and **2e**, Scheme 1) but not with $PhSe^+$.[7b]

It is noteworthy that the limited reactivity of the BTI/PhSeSePh system in CH_3CN with activated acetophenones becomes important in CH_3OH where the enol-derived pathway is now certainly favoured giving a completely different kind of product. In fact we have repeated the reaction of 4′-methoxyacetophenone in this solvent, working with a slight excess of BTI (1.2 mmol). After 30 min at 45°C, GC–MS analysis indicated a mixture of starting material and α-phenylseleno ketone together with an unknown product that did not contain PhSe. Moreover, no trace of product **3b** was detected in this reaction mixture. On adding an excess of BTI (0.6 mmol), both starting material and α-phenylseleno ketone were consumed and a careful investigation after purification showed that the product isolated (which did not show a molecular M^+ in the GC–MS spectrum recorded at 70 eV) was the α,α-dimethoxy carbonyl derivative, **5b**.[8] In light of this interesting result, we have extended our reaction to a series of methyl aryl ketones as depicted in Scheme 3. Total chemoselectivity was observed with only functionalisation of the methyl linked to the carbonyl being observed. Both 2′- and 4′-methoxyacetophenone provided compounds **5a** and **5c**,[9] respectively; 2′,4′-dimethoxyacetophenone furnished product **5d**.[10] As reported in Scheme 3 and Figure 1, this last reaction is more general and was applied to a series of alkyl aryl ketones. Compounds **5f**,[11] **5g**,[12] **5h**,[13] and **5k**,[14] were isolated in moderate to good yields starting from the parent ketones.[7b]



Scheme 2.



Scheme 3. (A) Electrophilic aromatic phenylselenenylation; (B) formation of α,α-dimethoxy ketones.

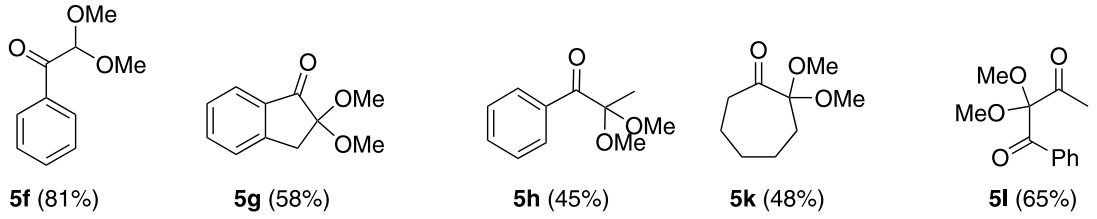


Figure 1. α,α-Dimethoxy ketones, obtained via pathway B in Scheme 2.

This type of transformation of methyl ketones employing activated selenium species in methanol is not completely new. In fact, in previous research, we prepared several monoprotected vicinal dicarbonyl compounds starting from a large variety of aliphatic and aromatic methylketones in the presence of diphenyl diselenide and an excess of ammonium peroxydisulfate in refluxing methanol.[11]

From these last results it emerged that both BTI and $(NH_4)_2S_2O_8$ are good oxidants, or activating agents, being able to generate, in situ, a very efficient electrophilic phenylselenenylated species. However it is important to note that the cheaper $S_2O_8^{2-}$ exclusively promoted the formation of several monoprotected keto aldeydes, starting from the corresponding methyl ketones, while BTI, as depicted in Scheme 3 and Figure 1, was able to transform ketones that contain a CH_2-group bonded to the carbonyl group, into the corresponding monoprotected vicinal diketones. As a matter of fact both peroxydisulphate anions and BTI are able to transform benzoylacetone into the corresponding α,α-dimethoxy derivative **5l**.[15]

Finally, we have observed that the only reactive intermediate that could be isolated starting from 4′-methoxyacetophenone, was the 1-(4′-methoxyphenyl)-2-(phenylseleno)ethanone. Exposure of this compound to BTI in methanol at 45°C furnished, in a few minutes, the corresponding 1-(4′-methoxyphenyl)-2,2-dimethoxy-

ethanone **5b** in good yields. No other intermediates have been observed during this last transformation. These results are still in agreement with those observed with the PhSeSePh/$(NH_4)_2S_2O_8$ system,[11] and suggest that probably a similar reaction pathway could be invoked. In conclusion, the chemistry of electrophilic iodine and selenium species continues to give very good results that, especially concerning the selenium behaviour, are still almost completely unpredictable. Much more could be done to understand the role of the I(III) species together with solvents to address the reactions observed.

In light of the growing interest in the chemistry of monoprotected vicinal dicarbonyl compounds,[16] the preparation of similar products using primary alcohols instead of methanol as protecting reagents is under way.

Acknowledgements

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7. **Typical procedures**: (a) *Iodination of aromatic ketones*: BTI (1.2 molar equiv.) was added at room temperature to a solution of ketone (1 mmol) and I_2 (0.6 molar equiv.), in anhydrous CH_3CN. The red–brown colour of the solution disappeared after a few minutes, and all the reactions described were complete in less than 2 h. After neutralisation with 0.1 M NaOH solution, the reaction mixture was extracted with *tert*-butylmethyl ether, washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude material which after purification on silica gel, using light petroleum as eluant to remove the iodobenzene derived from the reduction of BTI, followed by a mixture of light petroleum and *tert*-butylmethyl ether as eluant to recover the iodo derivatives. (b) *Phenylselenenylation of ketones*: in both series of experiments, 0.6 molar equiv. of $(PhSe)_2$ were employed working at 45°C. The BTI being added in the CH_3CN experiments, was 1.2 molar equiv., while 1.8 molar equiv. of BTI were necessary to obtain the α,α-dimethoxy carbonyl derivatives. All the reactions were complete in less than 4 h. Almost complete recovery of diphenyl diselenide was achieved from the preparation of α,α-dimethoxy carbonyl derivatives. For the preparation of monoprotected vicinal dicarbonyl compounds we tried to use a catalytic amount of diphenyldiselenide but the reactions were too slow and some of the starting ketones were consumed by the oxidant, to give unknown compounds. The products obtained were fully characterised by ^1H and ^{13}C NMR spectroscopy and MS. Selected experimental data: **2e**: solid, mp 83–86°C (uncorrected); δ_H ($CDCl_3$, 200 MHz): 7.85 (d, $J=7.5$ Hz, 1H), 6.65 (d, $J=7.5$ Hz, 1H), 3.80 (s, 3H), 2.9 (t, $J=6.4$ Hz, 2H), 2.65 (t, $J=6.4$ Hz, 2 H), 2.0 (quintet, $J=6.4$ Hz, 2H); δ_C ($CDCl_3$, 50 MHz): 197.3, 157.2, 140.8, 136.1, 115.1, 55.8, 39.3, 23.7, 21.9; GC–EIMS: m/z 302 (M^+) (87), 274 (30), 246 (23), 216 (13), 127 (39), 119 (51), 50 (100). **3b**: solid, mp 156–159°C (uncorrected); δ_H ($CDCl_3$, 300 MHz): 7.84 (dd, $J=8.5$, 2.1 Hz, 1H), 7.6 (m, 2H), 7.56 (d, $J=2.1$ Hz, 1H), 7.4 (m, 3H), 6.85 (d, $J=8.5$ Hz, 1H) 3.98 (s, 3H), 2.37 (s, 3H); δ_C ($CDCl_3$, 50 MHz): 196.4, 160.4, 135.6, 131.2, 129.6, 128.9, 122.8, 56.3, 26.2; GC–EIMS: m/z 306 (M^+) (4), 304 (2), 291 (2), 91 (6), 77 (22), 43 (100). **5e**: δ_H ($CDCl_3$, 200 MHz): 7.45 (d, $J=7.9$ Hz, 1H), 7.15 (t, $J=7.9$ Hz, 1H), 6.85 (d, $J=7.9$ Hz, 1H), 3.95 (s, 3H), 3.3 (s, 6H), 3.0 (t, $J=6.2$ Hz, 2H), 2.3 (t, $J=6.2$ Hz, 2H); δ_C ($CDCl_3$, 50 MHz): 191.7, 156.2, 132.0, 126.8, 119.3, 114.0, 96.6, 55.2, 49.3, 29.7, 20.0; GC–EIMS: m/z 236 (M^+) (12), 205 (11), 177 (100), 91 (32), 77 (27). **5g**:[12] solid, mp 50–53°C (uncorrected); δ_H ($CDCl_3$, 200 MHz) 7.65 (d, $J=7.6$ Hz, 1H) 7.45 (t, $J=7.6$ Hz, 1H), 7.22 (m, 2H), 3.37 (s, 6H), 3.15 (s, 2H); δ_C ($CDCl_3$, 50 MHz): 197.1, 149.1, 135.5, 133.5, 127.6, 126.3, 124.6, 101.6, 50.2, 38.1; GC–EIMS: m/z 192 (M^+) (5), 161 (10), 118 (10), 104 (28), 91 (100), 63 (60).
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