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Highly Efficient Arylation of Malonates with Diaryliodonium Salts

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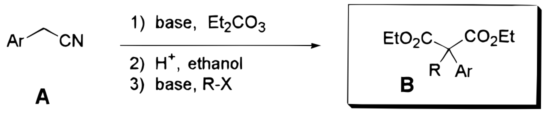
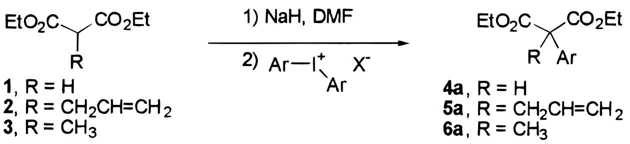
Unlike alkyl halides and their equivalents, aryl halides are not reactive enough to undergo intermolecular displacement reactions with metal enolates under normal conditions. Direct arylations of malonates have been accomplished by utilizing copper catalysts in low yields.[1] With the aid of palladium catalysts, however, malononitriles, phenylsulfonylacetonitriles, and ethyl cyanoacetates have been arylated in good to high yields.[2] It has been known that the presence of a cyano group in the enolates seemed to be crucial in the palladium catalyzed arylations.[3] Although there were a few reports on palladium-catalyzed intramolecular arylations of malonates or 1,3-diketones, no successful intermolecular arylation has yet been reported.[4] In most cases, dialkyl 2-arylmalonates (**B**) have been prepared in two steps: by condensation of arylacetonitriles (**A**) with diethyl carbonate, followed by esterification of the cyano group (eq 1).[5]



(1)

Recently, high valent iodonium salts have been revisited as reactive aryl iodide equivalents in organic reactions.[6] In early studies on high valent iodonium salts, some keto enolates reacted with diaryliodonium salts to give arylated ketones in good yields,[7] but ester enolates with the iodonium salts afforded the arylated esters only in low to moderate yields,[8] although the nucleophilicities of keto and ester enolates are almost identical. During our total synthesis of sesquiterpene laurene and its analogues,[9] we needed an efficient arylation methodology that could access structurally diverse arylated malonate esters. We thought that direct arylations of active methylene compounds could be achieved by employing more reactive electrophiles; here we wish to note our results from the synthetic point of view. Our first study was focused on the reaction of diethyl methylmalonate with diphenyliodonium tetrafluoroborate, as summarized in Table 1.

Table 1. Arylations of Malonates with Diaryliodonium Salts in DMF



	R	Ar_2IX	Temp (°C) /Time (h)	Products	Yield (%)
1	1	Ph_2IBF_4	70/4	**4a**	27
2		$(p\text{-Tol})_2IOTf$	70/4	**4b**	30
3[a]	2	Ph_2IBF_4	RT/2	**5a**	87
4		Ph_2IBF_4	RT/2	**5a**	83
5		$(p\text{-Tol})_2IOTf$	RT/2	**5b**	82
6[a]	3	Ph_2IBF_4	RT/2	**6a**	95
7		Ph_2IBF_4	RT/2	**6a**	86
8[a]		*p*-Tol-I[b]	120/15	**6b**	trace
9		$(p\text{-Tol})_2IOTf$	RT/2	**6b**	86

a: 5 mol% $Pd(PPh_3)_4$ was used as a catalyst.

b: This is not an iodonium salt but *p*-iodotoluene.

The sodium enolate derived from diethyl malonate (**1**) with diphenyliodonium tetrafluoroborate or ditolyliodonium triflate in dimethylformamide did not react at room temperature but reacted at 70 °C to give the corresponding phenylmalonate **4a** or *p*-tolylmalonate **4b**, respectively, in low yields (entries 1 and 2). Sodium enolates derived from diethyl allylmalonate (**2**) and diethyl methylmalonate (**3**), however, reacted smoothly with diphenyliodonium tetrafluoroborate at room temperature to give the corresponding phenyl malonates **5a** and **6a**, respectively. Diphenyliodonium triflate and ditolyliodonium triflate, prepared according to the known procedure,[10] also reacted with the three selected malonate enolates

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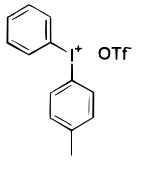
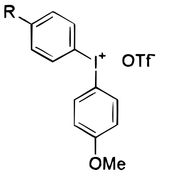
in the presence or absence of the palladium catalyst (entries 2, 5, and 9). Although $Pd(PPh_3)_4$ seemed to serve as a little better catalyst to produce the desired arylation, it might not be critical, indicating that the high valent iodonium salts should be reactive enough toward the enolate nucleophiles (entries 3 and 6). As expected, direct phenylation of diethyl methylmalonate (**3**) with *p*-iodotoluene under palladium catalysis occurred only slightly even at high temperature (120 °C).

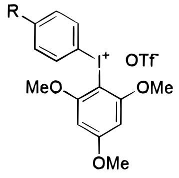
We expected that malonates could react better with an electron-deficient aryl group than with an electron-rich aryl group when unsymmetrical biaryl iodonium salts were employed. Thus, we prepared diverse aryl-substituted iodonium salts **7a**−**e** to determine chemoselectivity in aryl group transfers.



7a

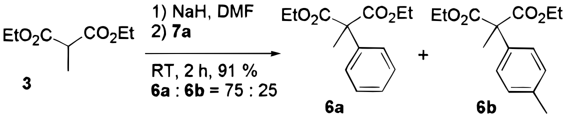


7b, R = H
7c, R = Me



7d, R = Me
7e, R = H

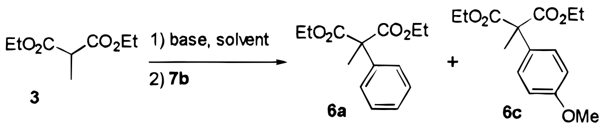
The arylations of diethyl methylmalonate (**3**) with diaryliodonium triflate **7a** in DMF proceeded cleanly to give a 3:1 mixture of the corresponding products **6a** and **6b** in 91% yield, as shown in eq 2.



(2)

Even a slight difference in the two aryl groups of diaryliodonium salt **7a** resulted in selective arylation, implying that the best selectivity could be obtained from a diaryliodonium salt possessing two electronically different aryl groups. In fact, the diaryliodonium salt **7b** with diethyl methylmalonate under similar conditions resulted in better chemoselective arylation, as summarized in Table 2.

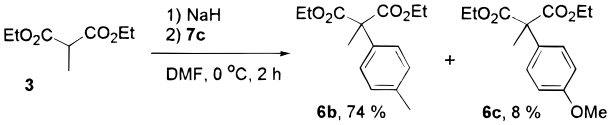
Table 2. Selective Arylation of Diethyl Methylmalonate with Diaryliodonium Salts



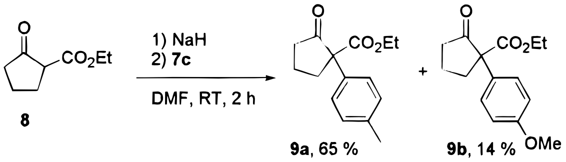
	Base, Solvent	Temp (°C) /Time (h)	Yield of 6a, %	Ratio 6a : 6c
1	NaH, DMF	RT/2	80	93 : 7
2	NaH, THF	RT/2	52	91 : 9
3	K(*t*-OBu), DMF	RT/2	71	83 : 17
4	LiH, DMF	RT/24	low	-
5	Et_3N, DMF	70/24	0	-
6[a]	Na_2CO_3, DMF	70/2	0	-

a: 5 mol% $Pd(PPh_3)_4$ was used as a catalyst.

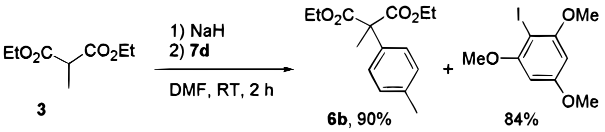
When iodonium salt **7b** reacted with the enolate of diethyl methylmalonate under the given conditions, the phenyl group was transferred about 10 times more rapidly than the *p*-methoxyphenyl group, giving products in ratios in the range of 91:9 to 93:7. Instead of sodium hydride, potassium *tert*-butoxide provided similar results but in a slightly lower selectivity of 83:17, presumably because the more ionic potassium enolate lowered the selectivity as a result of its higher reactivity. Other bases, such as triethylamine, sodium carbonate, and lithium hydride,[11] did not give the desired product. Among the solvents tried, DMF gave the best result for this arylation, whereas THF, ether, dichloromethane, and toluene were not optimal. With these preliminary results, we next attempted reaction of the iodonium salt **7c** with the malonate **3**. Under the optimal condition, as seen in eq 3, the arylated products **6b** and **6c** were isolated in 74% and 8% yields, respectively. This implies that the mixed iodonium salt **7c** could be an alternative to ditolyliodonium salt because of its ease of preparation and its thermal stability. The iodonium salt **7c** also reacted with β-ketoester (**8**) smoothly as seen in eq 4. The aryl group transfer occurred selectively in an 80:20 ratio when monitored by GC. The reaction was also clean enough to be synthetically useful to give the products **9a** and **9b** in 65% and 14% isolated yields, respectively. As an extreme case, (2,4,6-trimethoxyphenyl)(*p*-tolyl)iodonium salt (**7d**) was prepared. The reaction with the malonate enolate **3** afforded tolylmalonate (**6b**) as the sole arylated product along with 2,4,6-trimethoxyiodobenzene as a byproduct in 90% and 84% yields, respectively, as shown in eq 5.



(3)



(4)



(5)

Finally, we prepared (2,4,6-trimethoxyphenyl)phenyliodonium salt (**7e**) and reacted it with various enolates to explore the scope and the limitation of this present methodology, as summarized in Table 3. Note that only the phenyl group in the iodonium salt **7e** has been selectively transferred to the enolates derived from diethyl methylmalonate or α-alkylated β-ketoesters. Simple β-ketoesters **10a** and **10c**, however, did not undergo arylation under our conditions.

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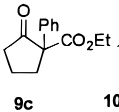
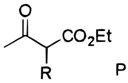
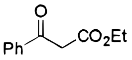
(11) Insoluble lithium hydride in DMF could not abstract a proton from the malonate **3**, because lithium hydride was still highly reactive when water was added into the reaction mixture.

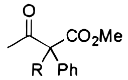
Table 3. Selective Arylation with (2,4,6-Trimethoxyphenyl)phenyliodonium Salt (7e) in DMF

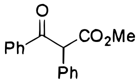
Reactants	Iodonium salts	Temp (°C) /Time (h)	Products(%)
3	**7e**	RT/2	**6a** (76)
8	**7e**	RT/2	**9c** (82)
10a	**7e**	RT/2	**11a** (~0)
10b	**7e**	RT/2	**11b** (59)
10c	**7e**	RT/2	**11c** (~0)


9c

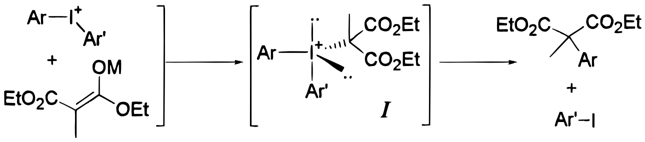

10a, R=H
10b, R=CH$_2$Ph


10c


11a, R=H
11b, R=CH$_2$Ph


11c

Scheme 1



Although a radical mechanism has been proposed in reactions involving high valent iodonium salts,[12] we could not detect any reduced products such as benzene, toluene, anisole, or 1,3,5-trimethoxybenzene. GC analysis of the reaction mixture after a short path filtration through a pad of silica gel showed only product peaks and their byproduct peaks corresponding to 4-methoxyiodobenzene or 4-iodotoluene. We reasoned that if a radical mechanism in these reactions is operating, the product arylmalonates possessing electron-donating methoxy groups should be a major product, because the 4-methoxyphenyl radical is more stable than the phenyl radical as a result of the electron-donating effect of the methoxy group. Based on the reverse selectivity observed in our study, we propose the addition−elimination mechanism shown in Scheme 1.

Our observations strongly support the unified mechanism, originally proposed by Grushin and co-workers,[13] in which the reactions of diaryliodonium salts with malonates should form tricoordinated iodine intermediates ***I*** like phosphines; the tricoordinated iodine intermediates ***I*** then undergo reductive elimination to give the products and aryl iodide.

In conclusion, the present study showed that 2-alkyl substituted malonates and α-alkyl substituted β-ketoesters were efficiently arylated with diaryliodonium salts in the presence of a base to give the corresponding aryl derivatives under mild conditions. Judging from the fact that the electron-deficient aryl group was selectively transferred to the nucleophiles, we propose that the present arylation reaction proceeds via ion-pair complexes to give tricoordinated iodine intermediates, which then undergo reductive elimination to yield the corresponding arylated malonates. A more detailed study, including the application to sesquiterpene laurene, is currently underway.

Experimental Section

General. All arylations were carried out under an atmosphere of dry argon. Commercial reagents were used as received without further purification. Diaryliodonium salts were prepared according to the known procedure.[10c] The analytical GLC to determine the product ratios was carried out with a Hewlett-Packard 5880A gas chromatography employing a DB-1 bonded-phase methylsilicon capillary column and flame-ionization detector. All products were purified by flash chromatography using silica gel 60 (70−230 mesh, Merck) and identified with ^{1}H and ^{13}C NMR spectral data obtained from a Varian Unity 300 MHz NMR spectrometer using tetramethylsilane as an internal standard.[5,8]

Typical Procedure. Arylation of Diethyl Methylmalonate (3). To a dry 2 mL DMF suspension of 60% sodium hydride (2.0 mmol) was added a 2 mL DMF solution of diethyl methylmalonate (**3**, 1.5 mmol) at 0 °C under argon atmosphere. To the enolate solution, after it was stirred for 10 min, was added a 2 mL DMF solution of diaryliodonium salt **7c** (2.0 mmol). The yellow reaction mixture was stirred until the reaction was complete by TLC and then quenched with water (2 mL) at 0 °C. After GC analysis, extractive workup and flash chromatography using a 10:90 mixture of ethyl acetate and hexane as an eluent afforded the corresponding products **6b** and **6c** in 74% and 8% yields, respectively. **6b**: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.31 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 4.20 (q, J = 7.0 Hz, 4H), 2.32 (s, 3H), 1.83 (s, 3H), 1.26 (t, J = 7.0 Hz, 6H). **6c**: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.26 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 4.18 (q, J = 7.0 Hz, 4H), 3.72 (s, 3H), 1.78 (s, 3H), 1.22 (t, J = 7.0 Hz, 6H).

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