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Iodine catalyzed Friedel–Crafts alkylation of electron-rich arenes with aldehydes: efficient synthesis of triarylmethanes and diarylalkanes

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ABSTRACT

lodine is shown to be an efficient catalyst for the Friedel–Crafts alkylation of arenes with a wide variety of aldehydes in toluene under 'open-flask' and mild conditions. In the presence of 10 mol % of iodine, the reaction of arenes with aromatic aldehydes gives the corresponding triarylmethane derivatives (TRAMs), regioselectively, in good to excellent yields. On the other hand, a series of diarylalkane derivatives is synthesized smoothly by reaction with aliphatic aldehydes.

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 $\begin{array}{c|c} Ar^{1}-H & \frac{l_{2} (10 \text{ mol}\%)}{1} \\ \textbf{1} & toluene, air \\ rt \\ RCHO \\ (R = alkyl) \\ \textbf{3} \end{array} \xrightarrow{\begin{array}{c} Ar^{2}CHO \\ Ar^{1} \\ Ar^{2} \\ Ar^{2} \\ Ar^{2} \\ Ar^{2} \\ Ar^{2} \\ Ar^{1} \\ Ar^{1} \\ R \\ \textbf{3} \end{array}$

Scheme 1. I2-catalyzed formation of TRAMs and diarylalkanes

(20 mol %) with a mixture of **1a** (2 equiv) and benzaldehyde (1 equiv) in CH₂Cl₂ afforded triarylmethane **2a**, regioselectively, in high yield (entry 1). By lowering the catalyst loading to 10 mol % (entry 2), the product **2a** was also obtained in similar vield, however, a longer reaction time was necessary. As anticipated, no reaction was observed in the absence of the iodine catalyst and both starting materials were recovered in quantitative yields (entry 3). The reaction under neat conditions (entry 4) gave the product in 53% yield. Reactions in different organic solvents and with propanal (entries 5-10) were studied. We found that a remarkable solvent effect existed in our iodine catalyzed reaction. Dichloromethane (entry 2) and toluene (entry 8) were the best solvents for good transformation in the case of benzaldehyde acceptors, while the other solvents were less effective and lower product yields of 39-81% were obtained (entries 5-7). Although reaction of the enolizable aldehyde acceptor, propanal, in CH₂Cl₂ gave a low yield of the diarylalkane **3a**, reaction in toluene was accomplished to afford **3a** in a high 89% yield.

Triarylmethanes (TRAMs) and diarylalkanes have attracted considerable attention¹ due to their varied biological activity as antiviral,² antitumor,³ antitubercular,⁴ antifungal,⁵ and anti-inflammatory agents.⁵ Moreover, these compounds have found widespread application in the chemical industry.^{1a,6} Methods for the synthesis of TRAMs and diarylalkanes have been developed^{7,8} which mainly centered on Friedel–Crafts alkylation of electron-rich arenes with aldehydes and their imines using AuCl₃/AgOTf,⁹ [Ir(-COD)Cl]₂–SnCl₄,^{5,10} Cu(OTf)₂/(±)-BINAP,¹¹ ZnBr₂/SiO₂,¹² FeCl₃,¹³ and Bi₂(SO₄)₃/TMSCl¹⁴ as the Lewis acids. However, most of these methods are multi-step processes, require harsh reaction conditions and are limited to non-enolizable aldehydes.

Molecular iodine has received considerable attention in organic and pharmaceutical syntheses due to its inexpensive, non-toxic, and environmentally friendly characteristics.¹⁵ Iodine has a high tolerance to air as well as moisture and can be easily removed from reaction systems. Moreover, the mild Lewis acidity associated with iodine has led to its use in various organic transformations in catalytic to stoichiometric amounts. In this paper, we report the molecular iodine catalyzed Friedel–Crafts alkylation of electronrich arenes using aromatic and enolizable aldehydes to generate either TRAMs or diarylalkanes, respectively, in high yields under mild reaction conditions (Scheme 1).

We first examined the reaction of 1,2,4-trimethoxybenzene (**1a**) with benzaldehyde using iodine as the catalyst in an open testtube at room temperature (Table 1). The initial reaction of iodine

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Table 1Optimization studies^a



Entry	Aldehyde	Catalyst (mol %)	Solvent	Time (h)	Product	Yield ^b (%)
1	PhCHO	20	CH_2Cl_2	48	2a	90
2	PhCHO	10	CH ₂ Cl ₂	72	2a	92
3	PhCHO	_c	CH ₂ Cl ₂	72	2a	d
4	PhCHO	10	_	18	2a	53 ^e
5	PhCHO	10	CH ₃ CN	72	2a	75
6	PhCHO	10	THF	72	2a	81
7	PhCHO	10	MeOH	72	2a	39
8	PhCHO	10	Toluene	72	2a	90
9	EtCHO	10	CH_2Cl_2	72	3a	36
10	EtCHO	10	Toluene	72	3a	89

^a Reaction conditions: **1a** (2 mmol), aldehyde (1 mmol), I₂, solvent (1 mL), room temperature.

^b Isolated yield.

^c Reaction conducted in the absence of iodine.

^d No reaction based on TLC analysis.

^e The reaction mixture solidified after stirring for 18 h.

The generality of the reaction was studied through experiments with different aldehydes as electrophiles (Table 2) under the optimum conditions (Table 1, entry 8).¹⁶ In the presence of 10 mol % of I₂, 1,2,4-trimethoxybenzene (2 equiv) reacted with a number of aromatic aldehydes possessing either electron-withdrawing (F, Cl, Br, and NO₂) or electron-donating (OMe) substituents to give the corresponding symmetric triarylmethanes **2b–g**, selectively, in good to excellent yields (entries 2–8). Due to the low reactivity

Table 2

I₂-catalyzed reaction of arene **1a** with various aldehydes^a

MeO Of Of	Me + RCHO $\frac{I_2 (10)}{tolue}$	0mol%) ene,air rt	OMe leO MeO R	OMe OMe OMe		
1a		2 (R=aryl) 3 (R=alkyl)				
Entry	R	Product	Time (h)	Yield ^b (%)		
1 2 3 4	$C_{6}H_{5}$ $4-FC_{6}H_{4}$ $4-ClC_{6}H_{4}$ $4-BrC_{6}H_{4}$	2a 2b 2c 2d	72 72 72 72	90 97 88 98		
5 6 7 8 9 10 11 12 13	$4-O_2NC_6H_4$ $3,4-(MeO)_2C_6H_3$ $3,4-(MeO)_2C_6H_3$ $3-MeOC_6H_4$ Et PhCH ₂ CH ₂ Me ₂ CHCH ₂ Me ₂ CH Ph(Me)CH Civalebecuel	2e 2f 2g 3a 3b 3c 3d 3e 2f	72 120 48 72 72 72 72 72 72 72 130	99 72 90° 87 89 80 87 95 99		

 a Reaction conditions: 1a (2 mmol), aldehyde (1 mmol), I_2 (10 mol %), toluene (1 mL), room temperature.

^b Isolated vield.

^c The reaction was carried out at 60 °C.

of 3,4-dimethoxybenzaldehyde, increasing the reaction temperature to 60 °C gave a significant increase in the yield of **2f** in a shorter reaction time (entries 6 and 7). Furthermore, the corresponding diarylalkane adducts **3a–f** were smoothly obtained in 80–99% yields when various aliphatic aldehydes were used (entries 9– 14).¹⁶

We next explored the iodine catalyzed Friedel-Crafts alkylation of various arenes as well as 2-methylfuran with either aromatic or aliphatic aldehydes for the synthesis of the corresponding TRAMs or diarylalkanes, respectively. The results presented in Table 3 show that all the reactions gave selective formation of triarylmethane and diarylalkane derivatives. The reactions of mono-, di- or trimethoxy substituted arenes with 4-nitrobenzaldehyde or 3-phenylpropanal afforded the corresponding TRAMs **2h-j** or diarylalkanes **3g-i**, respectively, in moderate to high yields (entries 1-4 and 6-10). The reaction of heteroaromatic 2-methylfuran with 3phenylpropanal gave the alkylated diheteroarylalkane 3j in 84% yield (entry 11). Additionally, the reaction of 2-methylfuran was also performed in water as the reaction medium due to its many advantages from economical, environmental, and safety standpoints.¹⁷ Gratifyingly, the reaction succeeded to provide the desired product 3j in an excellent 99% yield (entry 12). Compound **2k** which has been reported to show significant antiviral activity⁵ was synthesized smoothly in an excellent 92% yield by condensation of phenol with 4-chlorobenzaldehyde (entry 5).

In summary, we have demonstrated an efficient molecular iodine catalyzed Friedel–Crafts alkylation of electron-rich arenes with a wide variety of aldehydes in toluene under 'open flask' and mild conditions. Typically, the reaction of arenes with aromatic aldehydes provides the corresponding triarylmethane derivatives (TRAMs), regioselectively, in good to excellent yields. In addition, a series of diarylalkane derivatives has been smoothly synthesized by reaction with aliphatic aldehydes. Further investigations on the scope and limitations of this reaction are in progress.

Table 3

I₂-catalyzed reaction of various arenes with aliphatic and aromatic aldehydes^a

		Ar-H + RCHO	I ₂ (10 mol%) Ar Ar			
		1	rt R aryl)			
Entry	Ar-H	RCHO	Product		Time (h)	Yield ^b (%)
1 2	1,3,5-Trimethoxybenzene 1,3,5-Trimethoxybenzene	4-0 ₂ NC ₆ H ₄ CHO 4-0 ₂ NC ₆ H ₄ CHO	MeO MeO MeO NO ₂	2h 2h	24 24	82 93°
3	1,2,3-Trimethoxybenzene	4-0 ₂ NC ₆ H ₄ CHO	MeO MeO MeO MeO MeO MeO MeO MeO MeO MeO	2i	72	47 ^c
4	1,2-Dimethoxybenzene	4-O ₂ NC ₆ H ₄ CHO	MeO MeO NO ₂	2j	72	63°
5	Phenol	CIC ₆ H₄CHO	HO CI	2k	12	92°
6 7	1,2,3-Trimethoxybenzene 1,2,3-Trimethoxybenzene	PhCH ₂ CH ₂ CHO PhCH ₂ CH ₂ CHO	MeO MeO MeO MeO Ph	3g 3g	72 48	66 78°
8 9	1,2-Dimethoxybenzene 1,2-Dimethoxybenzene	PhCH ₂ CH ₂ CHO PhCH ₂ CH ₂ CHO	MeO MeO Ph	3h 3h	72 24	49 78°
10	Anisole	PhCH ₂ CH ₂ CHO	MeO OMe	3i	72	76
11 12	2-Methylfuran 2-Methylfuran	PhCH ₂ CH ₂ CHO PhCH ₂ CH ₂ CHO	Me O Me	3j 3j	22 24	84 99 ^d

 a Reaction conditions: arene 1 (2 mmol), aldehyde (1 mmol), I₂ (10 mol %), toluene (1 mL), room temperature. b Isolated yield. c The reaction was carried out at 60 °C. d The reaction was carried out in H₂O (1 mL).

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- Typical experimental procedure: To a toluene solution (1 mL) of arene 1 16. (2 mmol) and aldehyde (1 mmol) in a test-tube open to air at room temperature was added molecular iodine (0.1 mmol, 10 mol %). The reaction was stirred until completion (TLC analysis). The reaction mixture was quenched with aqueous $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 $(2 \times 10 \text{ mL})$. The combined organic layer was washed with brine (10 mL), dried over anhydrous MgSO4, concentrated and purified by radial chromatography (hexanes/EtOAc as eluent) to give 2 or 3. Spectral data for 2a: ¹H NMR (400 MHz, CDCl₃): 7.28-7.23 (m, 2H), 7.19-7.15 (m, 1H), 7.07 (d, 2H, J = 7.2 Hz), 6.56 (s, 2H), 6.45 (s, 2H), 6.10 (s, 1H), 3.89 (s, 6H), 3.67 (s, 6H), 3.65 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): 151.6, 148.0, 144.3, 142.7, 129.0, 128.0, 125.8, 124.5, 114.6, 98.4, 57.0, 56.7, 56.1, 42.6; IR (Nujol): 2926, 2833, 1608, 1511, 1465, 1396, 1318, 1250, 1207, 1179, 1037 cm⁻¹; MS (EI): *m/z* (%): 425 (25), 424 (M⁺, 100), 393 (81), 181 (43), 151 (53), 91 (11); HRMS (ESI-TOF) calcd for C₂₅H₂₈O₆Na 447.1784, found: 447.1760. For **3b**: ¹H NMR (400 MHz, CDCl₃): 7.31-7.27 (m, 2H), 7.21-7.19 (m, 3H), 6.89 (s, 2H), 6.56 (s, 2H), 4.69 (t, 1H, J = 7.7 Hz), 3.89 (s, 6H), 3.84 (s, 6H), 3.78 (s, 6H), 2.67 (m, 2H), 2.35 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): 151.8, 147.8, 142.9, 128.5, 128.2, 125.6, 125.0, 113.0, 98.5, 56.8 (2 × C), 56.1, 37.0, 36.5, 34.5; IR (Nujol): 2937, 1608, 1510, 1465, 1206, 1037 cm⁻¹; MS-EI: m/z (%): 452 (M⁺, 30), 347 (81), 181 (100); HRMS (ESI-TOF) calcd for C₂₇H₃₂O₆ 452.2199, found: 452.2181.
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