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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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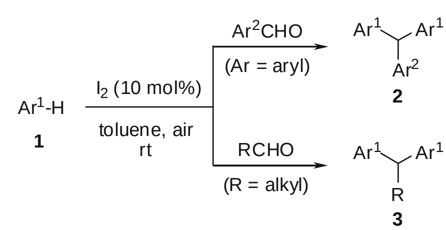
ABSTRACT

Iodine 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.

Triarylmethanes (TRAMs) and diarylalkanes have attracted considerable attention[1] 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 $AuCl_3$/AgOTf,[9] $[Ir(COD)Cl]_2$–$SnCl_4$,[5,10] $Cu(OTf)_2$/(±)-BINAP,[11] $ZnBr_2/SiO_2$,[12] $FeCl_3$,[13] and $Bi_2(SO_4)_3$/TMSCl[14] 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 electron-rich 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 test-tube at room temperature (Table 1). The initial reaction of iodine



Scheme 1. I_2-catalyzed formation of TRAMs and diarylalkanes

(20 mol %) with a mixture of **1a** (2 equiv) and benzaldehyde (1 equiv) in CH_2Cl_2 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 yield, 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 CH_2Cl_2 gave a low yield of the diarylalkane **3a**, reaction in toluene was accomplished to afford **3a** in a high 89% yield.

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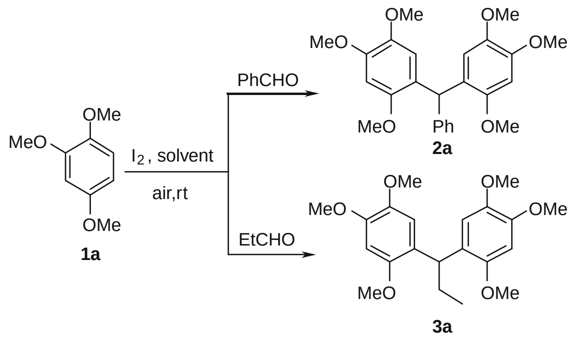
Table 1
Optimization studies[a]

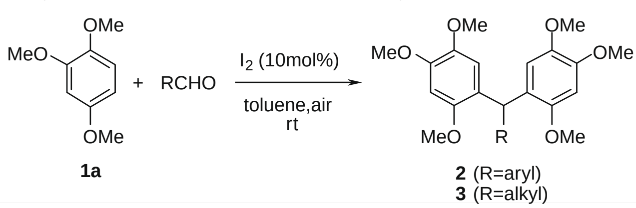


Entry	Aldehyde	Catalyst (mol %)	Solvent	Time (h)	Product	Yield[b] (%)
1	PhCHO	20	CH_2Cl_2	48	**2a**	90
2	PhCHO	10	CH_2Cl_2	72	**2a**	92
3	PhCHO	–[c]	CH_2Cl_2	72	**2a**	–[d]
4	PhCHO	10	–	18	**2a**	53[e]
5	PhCHO	10	CH_3CN	72	**2a**	75
6	PhCHO	10	THF	72	**2a**	81
7	PhCHO	10	MeOH	72	**2a**	39
8	PhCHO	10	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), I_2, 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 I_2, 1,2,4-trimethoxybenzene (2 equiv) reacted with a number of aromatic aldehydes possessing either electron-withdrawing (F, Cl, Br, and NO_2) 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 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]

Table 2
I_2-catalyzed reaction of arene **1a** with various aldehydes[a]



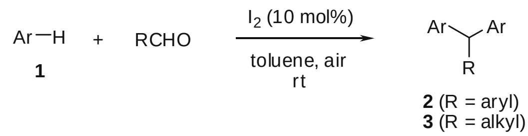
Entry	R	Product	Time (h)	Yield[b] (%)
1	C_6H_5	**2a**	72	90
2	4-FC_6H_4	**2b**	72	97
3	4-ClC_6H_4	**2c**	72	88
4	4-BrC_6H_4	**2d**	72	98
5	4-$O_2NC_6H_4$	**2e**	72	99
6	3,4-$(MeO)_2C_6H_3$	**2f**	120	72
7	3,4-$(MeO)_2C_6H_3$	**2f**	48	90[c]
8	3-$MeOC_6H_4$	**2g**	72	87
9	Et	**3a**	72	89
10	$PhCH_2CH_2$	**3b**	72	80
11	Me_2CHCH_2	**3c**	72	87
12	Me_2CH	**3d**	72	95
13	Ph(Me)CH	**3e**	130	99
14	Cyclohexyl	**3f**	72	99

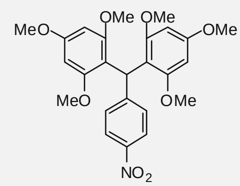
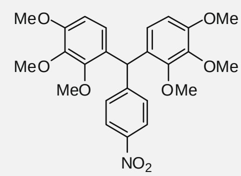
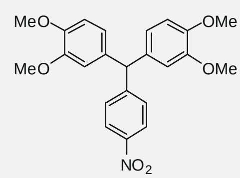
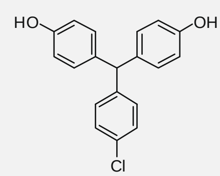
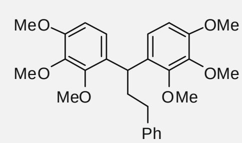
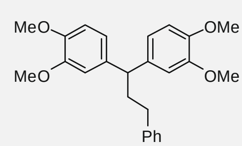
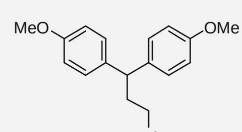
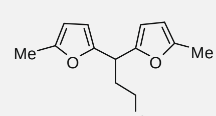
[a] Reaction conditions: **1a** (2 mmol), aldehyde (1 mmol), I_2 (10 mol %), toluene (1 mL), room temperature.
[b] Isolated yield.
[c] The reaction was carried out at 60 °C.

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 3-phenylpropanal 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 activity[5] 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
I_2-catalyzed reaction of various arenes with aliphatic and aromatic aldehydes[a]



Entry	Ar-H	RCHO	Product		Time (h)	Yield[b] (%)
1	1,3,5-Trimethoxybenzene	4-$O_2NC_6H_4CHO$		**2h**	24	82
2	1,3,5-Trimethoxybenzene	4-$O_2NC_6H_4CHO$		**2h**	24	93[c]
3	1,2,3-Trimethoxybenzene	4-$O_2NC_6H_4CHO$		**2i**	72	47[c]
4	1,2-Dimethoxybenzene	4-$O_2NC_6H_4CHO$		**2j**	72	63[c]
5	Phenol	ClC_6H_4CHO		**2k**	12	92[c]
6	1,2,3-Trimethoxybenzene	$PhCH_2CH_2CHO$		**3g**	72	66
7	1,2,3-Trimethoxybenzene	$PhCH_2CH_2CHO$		**3g**	48	78[c]
8	1,2-Dimethoxybenzene	$PhCH_2CH_2CHO$		**3h**	72	49
9	1,2-Dimethoxybenzene	$PhCH_2CH_2CHO$		**3h**	24	78[c]
10	Anisole	$PhCH_2CH_2CHO$		**3i**	72	76
11	2-Methylfuran	$PhCH_2CH_2CHO$		**3j**	22	84
12	2-Methylfuran	$PhCH_2CH_2CHO$		**3j**	24	99[d]

[a] Reaction conditions: arene **1** (2 mmol), aldehyde (1 mmol), I_2 (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 H_2O (1 mL).

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16. *Typical experimental procedure*: To a toluene solution (1 mL) of arene **1** (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 (2×10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, concentrated and purified by radial chromatography (hexanes/EtOAc as eluent) to give **2** or **3**. Spectral data for **2a**: ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{28}O_6Na$ 447.1784, found: 447.1760. For **3b**: ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 151.8, 147.8, 142.9, 128.5, 128.2, 125.6, 125.0, 113.0, 98.5, 56.8 ($2 \times C$), 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 $C_{27}H_{32}O_6$ 452.2199, found: 452.2181.
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