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Room temperature MgI_2-catalyzed Friedel–Crafts reaction between electron-rich (het)arenes and ethyl glyoxylate

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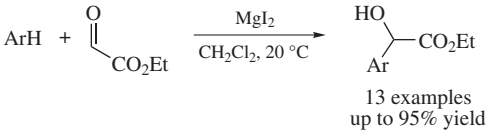
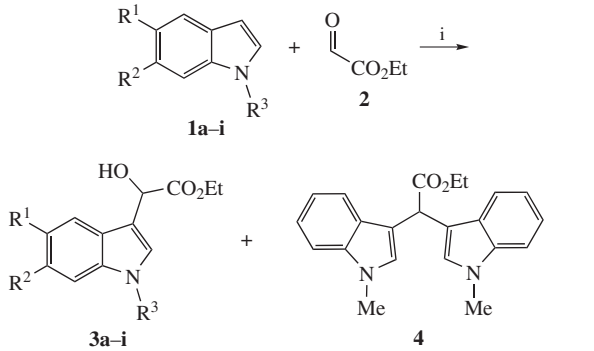
Magnesium iodide-catalyzed addition of electron-rich (het)arenes to ethyl glyoxylate proceeds at room temperature with high chemoselectivity to afford ethyl 2-(het)aryl-2-hydroxyacetates in yields up to 95%.



The Friedel–Crafts reaction with carbonyl compounds (Friedel–Crafts hydroxyalkylation) is one of the fundamental organic reactions known since the end of the 19th century. For example, bakelite synthesis by polycondensation of phenol with formaldehyde is the most valuable example of this reaction.[1] Other aromatic and carbonyl compounds can also enter into such a hydroxyalkylation.[2–17]

The 3-substituted indole motif commonly occurs among natural and biologically active compounds.[18] The addition of indole **1a** to ethyl glyoxylate **2** is not studied sufficiently although their adduct **3a** should be a promising indole analogue of mandelic acid ester (Scheme 1). The published data on such a transformation are scarce.[19–23]

In our previous study of the Friedel–Crafts reaction,[24–29] we found that addition of indole to activated olefins could be catalyzed by magnesium iodide,[24] a very effective Lewis acid. We hypothesized that the unique properties of MgI_2 could also show up in the reaction between indole and ethyl glyoxylate. Herein, we present the addition of indole and other electron-rich (het)arenes to ethyl glyoxylate catalyzed by MgI_2.



a $R^1 = R^2 = R^3 = H$, 80%
b $R^1 = F$, $R^2 = R^3 = H$, 92%
c $R^1 = Cl$, $R^2 = R^3 = H$, 90%
d $R^1 = Br$, $R^2 = R^3 = H$, 80%
e $R^1 = Me$, $R^2 = R^3 = H$, 87%
f $R^1 = MeO$, $R^2 = R^3 = H$, 89%
g $R^1 = NO_2$, $R^2 = R^3 = H$, 70%
h $R^1 = R^3 = H$, $R^2 = CO_2Me$, 95%
i $R^1 = R^2 = H$, $R^3 = Me$, 58%

Scheme 1 *Reagents and conditions:* i, **1a–i** (0.5 mmol), **2** (0.25 mmol), MgI_2 (0.025 mmol), CH_2Cl_2 (0.5 ml), 20 °C, 24 h (for **1f**, 18 h and for **1g**, 30 h). Yields are preparative after column chromatography.

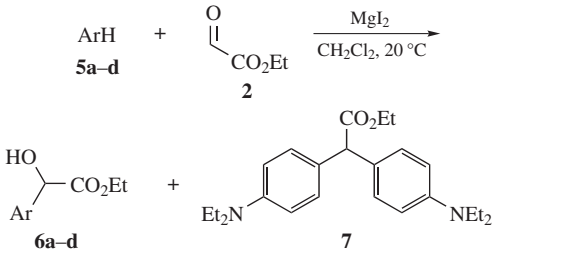
We used the previously optimized conditions (10 mol% MgI_2 in CH_2Cl_2)[24] at room temperature for the addition of unsubstituted indole **1a** to ethyl glyoxylate **2**. It is known that bis-adduct **4a** (see Scheme 1) can also be formed in this reaction under Lewis acid catalysis (for the mechanism, see ref. 30 and Scheme S1, Online Supplementary Materials). Surprisingly, under our conditions no bis-adduct was formed, and hydroxy ester **3a** was obtained in 80% yield (see Scheme 1).

To evaluate the scope of the reaction, we studied the effect of substituents in the indole ring on outcome of the process. The introduction of fluorine or chlorine into 5-position of the indole ring leads to increase in the yields of products **3b**,**c** to 92 and 90%, respectively (see Scheme 1), while in the case of 5-bromoindole **1d** the yield of product **3d** is the same as for **3a**. To our surprise, the introduction of electron-donating substituents into 5-position raises the yields of products **3e**,**f** to 87 and 89%, respectively. The introduction of electron-withdrawing NO_2 group (indole **1g**) led to a lower 70% yield of the adduct **3g**. In case of 6-methoxycarbonylindole **3h**, the yield of diester **3h** was almost quantitative. On moving to 1-methyl-1*H*-indole **1i**, yield of mono-adduct **3i** dropped to 58% due to formation of bis-adduct **4i** (see Scheme 1) which was detected by ^1H NMR but was not isolated.

As compared to other Lewis acids,[19–22] magnesium iodide has advantages in the addition of **1a** to **2**. In the cases of $SmI_2(THF)_2$, $Ti(OPr^i)_4$/*S*-BINOL, $LiCl/(CF_3)_2CHOH$ (Table 1, entries 1–3) the yields of product **3a** are lower, while for systems $Ti(OPr^i)_4$/*S*-BINOL (entry 2) and $Sc(OTf)_3$ with sophisticated *N*,*N*′-dioxide ligands (entry 4) high yields were achieved only at lower temperatures. Moreover, the advantage of our procedure is the possibility to

Table 1 Influence of the catalyst nature on the yield of product **3a** in the addition of **1a** to **2**.

Entry	Catalyst	*T*/°C	Inert atmosphere	Yield of **3a** (%)	Reference
1	$SmI_2 \cdot (THF)_2$	20	–	38	19
2	$Ti(OPri)_4$/*S*-BINOL	0	+	72	20
3	$LiCl/(CF_3)_2CHOH$	20	+	74	21
4	$Sc(OTf)_3$/ *N*,*N*′-dioxide ligand	0	+	90	22
5	MgI_2	20	–	80	This work



a Ar = 2,4-$(MeO)_2C_6H_3$, 32%
b Ar = 2,4,6-$(MeO)_3C_6H_2$, 75%
c Ar = 5-methylfuran-2-yl, 70%
d Ar = 4-$Et_2NC_6H_4$, 42% (for **7**, 21%)

Scheme 2

carry out the reaction under atmospheric air (entry 5). On scaling the reaction up to 1 g of indole **1a**, the yield of adduct **3a** was as good as 730 mg (79%).

Further on, we investigated addition of other (het)arenes using our procedure. Polymethoxybenzenes **5a**,**b** react with ethyl glyoxylate **2** to form the corresponding alcohols **6a**,**b** in 32 and 75% yields, respectively (Scheme 2). 2-Methylfuran **5c** gives the product **6c** in 70% yield.

The similar reaction of *N*,*N*-diethylaniline **5d** affords a 2 : 1 mixture of mono- and bis-adducts **6d** and **7** (see Scheme 2) in total 63% yield (calculated from ^{1}H NMR). Pyrrole and *N*-methylpyrrole form complex mixtures of products of mono- and polyalkylation. These mixtures cannot be separated by column chromatography.

In conclusion, we have developed an efficient convenient procedure for the preparation of indole analogues of mandelic acid esters. The reaction is promoted by magnesium iodide serving as the Lewis acid and proceeds at room temperature. The method can be extended to some other electron-rich (het)arenes to obtain new promising compounds for biomedical applications.[31]

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Online Supplementary Materials

Supplementary data associated with this article (procedures and characteristics of products) can be found in the online version at doi: 10.1016/j.mencom.2018.07.030.

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