An efficient $TiCl_4$-catalysed method for the synthesis of *para*-substituted aromatic aldehydes

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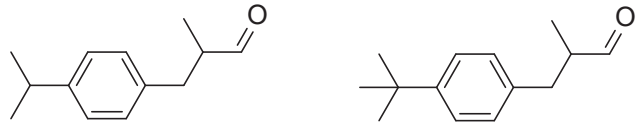
An efficient and highly selective synthesis of *para*-substituted aromatic aldehydes has been achieved by $TiCl_4$-catalysed Friedel–Crafts alkylation of monosubstituted benzenes with methacrolein diacetyl acetal.

Keywords: $TiCl_4$, Friedel–Crafts alkylation, aromatic aldehydes

A *para*-substituted aromatic aldehyde is an important substructure in both natural products and therapeutic agents. Cyclamen aldehyde (Fig.1, **1**), a typical *para*-substituted aromatic aldehyde, is often used as an intermediate in efficient syntheses of various compounds such as Sulindac analogues,[1] α- and β-amino acids and β-lactams,[2] bisabolane sesquiterpenes[3] and tricyclic steroid precursors.[4] It is also used as a surrogate for lily aldehyde (Fig.1, **2**), which is frequently used in detergents and soaps.[5]

Cyclamen aldehyde has been prepared using several methods (Scheme 1, A–D). It was first prepared about 90 years ago by base-catalysed aldol condensation of 4-isopropylbenzaldehyde with propanal (Method A) using inorganic bases (NaOH, KOH)[6] and more recently using heterogeneous catalysts such as Al_2O_3–MgO[7] or a Ru/C combination.[8] It has also been prepared by palladium-catalysed coupling reactions (Methods B and C).[9-11] Scriabine[12] reported a convenient and much cheaper way by reacting cumene with methacrolein at –15 °C catalysed by a $TiCl_4/BF_3$–Et_2O system, but with only a low yield of 31% (Method D) . The yields were generally poor using these methods, and the ratio of isomers was not usually discussed.



Cyclamen aldehyde, **1** Lily aldehyde, **2**

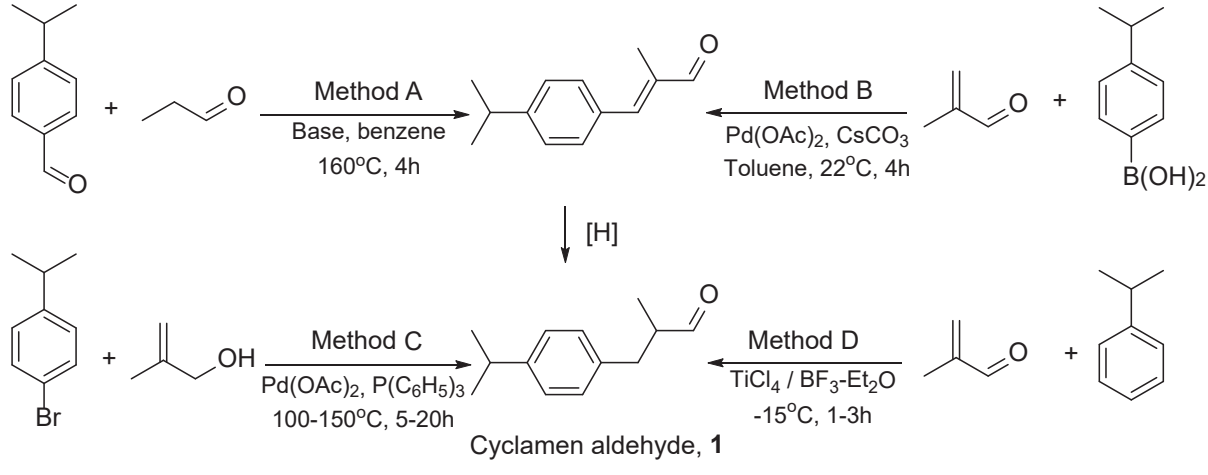
Fig. 1

As is well known, Friedel–Crafts alkylation of aromatic compounds is an important synthetic method to construct C–C bonds.[13,14] The reaction is carried out between olefins and various substituted aromatics, especially aromatics with electron-donating groups such as alkyl, alkoxy or halogen groups. However, there are only a few reports on the reaction of aromatics with α,β-unsaturated aldehydes such as methacrolein because of the poor selectivity or yields. For example, Yamada[15] reported the $Pd(OAc)_2$-catalysed coupling reaction of substituted aromatics with α,β-unsaturated aldehydes, but observed with poor selectivity (*o:m:p*=9:51:40). Evans[16] reported a similar reaction using Friedel–Crafts alkylation in the presence of bis(oxazolinyl)pyridine–scandium(III) triflate complexes. The catalyst was prepared using a complex method which limits its application. Recently, Shirai and coworkers[17] reported a new method of reacting aromatics with α,β-unsaturated aldehyde diacetyl acetals using $TiCl_4$ as catalyst. One such reactant was methacrolein diacetyl acetal. They also claimed that methacrolein diacetyl acetal reacted with 1,4-benzodioxan in the presence of BF_3·Et_2O. However, the ratio of *o, p*-isomers was not discussed.

We now report the efficient selective preparation of *para*-substituted aromatic aldehydes using a $TiCl_4$-catalysed reaction of aromatics with methacrolein diacetyl acetal.

Results and discussion

Several Friedel–Crafts catalysts were evaluated in order to optimise the reaction. As a model, the reaction of cumene **3** and methacrolein diacetyl acetal **4** was investigated and the yields and ratios of the *o*- and *p*-alkylation products **1** were tabulated



Scheme 1

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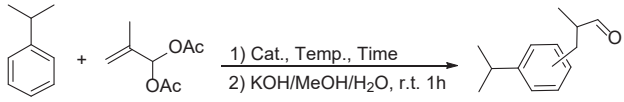
Table 1 Yields of the *o*- and *p*-alkylation products **1** of cumene **3** using methacrolein diacetyl acetal **4** in combination with a Friedel–Crafts catalyst under various conditions[a]



3 **4** **1**

Entry	Cat.	$n_{cat.}$:n_2	Temp/°C	Time/h	Yield of **1**/%[b]	Ratio of **1** (*p*:*o*)[c]
1	–	–	25	6	N.D.	–
2	$SnCl_4$	1.5:1	–10	3	61	94.1:5.9
3	BF_3·Et_2O	0.5:1	–10	3	37	89.0:11.0
4	$AlCl_3$	2:1	–10	6	30	82.5:17.5
5	$ZnCl_2$	1:1	–10	24	N.D.	–
6	$FeCl_3$	1:1	25	48	N.D.	–
7	HOTf	1:1	–10	24	10	87.2:12.8
8[d]	$M(OTf)_n$	1:1	r. t.	48	N.D.	–
9	$TiCl_4$	0.5:1	–10	3	35	89.3:10.7
10	$TiCl_4$	1:1	–10	3	74	89.9:10.1
11	$TiCl_4$	2:1	–10	3	87	91.2:8.8
12	$TiCl_4$	1.5:1	–5	3	73	83.3:16.7
13	$TiCl_4$	1.5:1	0	3	79	72.4:27.6
14	$TiCl_4$	1.5:1	–10	1	61	95.7:4.3
15	$TiCl_4$	1.5:1	–10	2	77	95.2:4.8
16	$TiCl_4$	1.5:1	–10	3	87	94.3:5.7
17	$TiCl_4$	1.5:1	–10	4	88	92.1:7.9
18	$TiCl_4$	1.5:1	–15	3	88	94.1:5.9
19	$TiCl_4$	1.5:1	–20	3	85	93.8:6.2

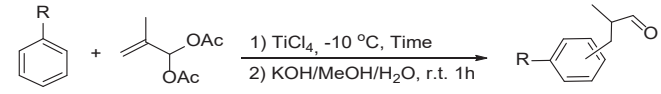
[a]Reaction conditions: **4** (3.4 g, 20 mmol), **3** (19.2 g, 0.16 mol), MeOH/KOH/H_2O (4 mL, mass ratio: 4:2:2).
[b]Yield of the isolated product.
[c] Determined by GC.
[d] M = Cu, La, Ye.

(Table 1). As expected, no product was obtained even after 6 h when catalyst was absent (entry 1). Some catalysts gave moderate to poor yields when screened at temperatures ranging from –10 to 25 °C (entries 2–8). As can be seen, however, $TiCl_4$ proved to be the most efficient catalyst under a variety of conditions (entries 9–19). Indeed, at a ratio of reactant to catalyst of 1:1.5, a high yield of 87% in 3 h at –10 °C was achieved (entry 16). Neither extending the reaction time to 4h, nor running the reaction at –15 °C improved the yield (entries 17 and 18).

On the basis of these results, several substituted benzenes were subjected to the optimal conditions, and *para*-substituted aromatic aldehydes were obtained major products as moderate to good yields in most cases. The results are listed in Table 2.

Similar yields were obtained when the reaction was carried out using alkyl substituted benzenes **3a–g** (entries 1–7). It appears, however, that the reaction only occurs when R is an electron-donating group, for there was no reaction when R was an electron-withdrawing group (–Br, –Cl, $–COCH_3$, $–NHCOCH_3$) even when the reaction time was extended to 6h (entries 9–11). When isopropylbenzene, *t*-butylbenzene, isobutylbenzene, *t*-amylbenzene were used (entries 4–7), the yields of *para*-substituted products was much greater than those of the *ortho*-substituted products. It proceeded in high regioselectivity when R was a bulky group (entries 5–7). On the other hand, it very good yield (87%) was obtained when R was a relatively small alkyl group, such as isopropyl (entry 4).

Table 2 Yields of the *o*- and *p*-alkyation products **1a–k** of monosubstituted benzenes **3a–k** using methacrolein diacetyl acetal **4** catalysed by $TiCl_4$ [a]



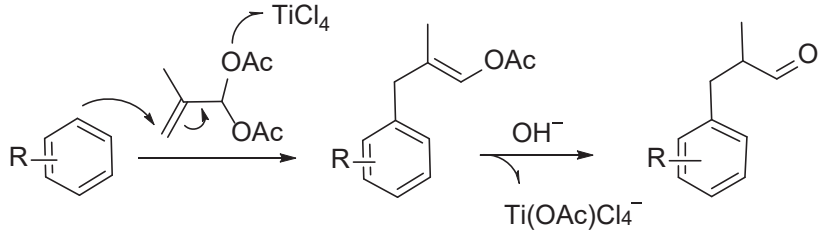
3a–k **4** **1a–k**

Entry	R	Time/h	Product	Yield of **1**[b] /%	ratio(*p*-:*o*-)[c]
1	–H	4	**1a**	71	–
2	Me	4	**1b**	80	72.9:27.1[d]
3	Et	3	**1c**	81	67.3:32.7[d]
4	*i*-Pr	3	**1d**	87	94.3:5.7
5	*t*-Bu	3	**1e**	79	96.3:3.7
6	*i*-Bu	4	**1f**	73	86.8:13.2
7	Amyl	4	**1g**	66	>99:1
8	$–OCH_3$	3	**1h**	65	93.3:6.7
9	–X[e]	6	**1i**	N.D.	–
10	$–COCH_3$	6	**1j**	N.D.	–
11	$–NHCOCH_3$	6	**1k**	N.D.	–

[a] Reaction conditions: **4** (3.4 g, 20 mmol), **3** (0.16 mol), $TiCl_4$ (5.7 g, 30 mmol), –10°C. MeOH/KOH/H_2O (4 mL, mass ratio: 4:2:2).
[b] Yield of the isolated product.
[c] Determined by GC.
[d] Determined by ^{1}H NMR.
[e] X = Cl, Br.

A possible reaction mechanism is shown in Scheme 2. The catalytic effect of $TiCl_4$ appeared to be unique in this reaction, and this may be related to its strong chelating properties which gave rise to easily formed five- or six-coordination compounds in the reaction. This might also explain why large substituted aromatics such as *t*-amyl benzene **3g** gave only moderate yields of alkylation products (entry 7, 66%).

In conclusion, we have described a practical and highly selective way to prepare *para*-substituted aromatic aldehydes by Friedel–Crafts alkylation of benzenes with diethyl acetals of α,β-unsaturated aldehydes. These results indicate that $TiCl_4$ functions well in this type of Friedel–Crafts alkylation. The optimal reaction conditions for the maximum yield of cyclamen aldehyde were found which may be used for the industrial preparation of cyclamen aldehyde.



Scheme 2

Experimental

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained using a Varian Mercury plus 400 spectrometer (Varian, CA, USA) equipped with a 5 mm ID probe or a 5 mm ASW probe using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. GC spectra were obtained on a SHIMADZU GC-SPL-2010 Plus instrument with rtx-1 as the GC column. Mass spectra were measured with a Thermo Finnigan LC Advantage (Agilent 1100). GC-MS spectra were measured with a GCT Premier GC/MS using ESI or EI (electrospray ionization) techniques.

Synthesis of methacrolein diacetyl acetal **4***; general procedure*

A dry 100-mL flask was charged with Ac_2O (51.0 g, 0.5 mol) and $BF_3{\cdot}Et_2O$ (0.07 g, 0.5 mmol), cooled to –10°C, and then methacrolein (35.0 g, 0.5 mol) was added over 20 min. The mixture was the stirred at –10°C for 3 h. Methacrolein diacetyl acetal **4** was then easily obtained by vacuum distillation (20 mmHg, 72.5g, 85%).

2-Methacrolein diacetyl acetal (**4**): Oil; ^{1}H NMR δ 7.05 (1H, s, CH), 5.23 (1H, qua, CH_{2a}), 5.06 (1H, qui, CH_{2b}), 2.08 (6H, s, CH_3), 1.78 (3H, t, CH_3). ^{13}C NMR δ 168.3, 138.5, 116.1, 90.6, 20.8, 16.6; MS (ESI): *m/z* = 195[M+Na]$^+$.

Synthesis of para-substituted aromatic aldehydes **1a–k***; general procedure*

A dry 50-mL flask was charged with methacrolein diacetyl acetal **4** (3.4 g, 20 mmol) and a substituted benzene **3** (160 mmol). Then, $TiCl_4$ (5.7 g, 30 mmol) was added into the mixture dropwise at–10 °C over 30 min. The mixture was stirred at –10 °C for further 1–4 h. After the reaction had finished, the mixture was poured with agitation onto dilute hydrochloric acid (1M). The brownish-red solution became decolourised, and was washed with water. The organic layer was added into solution MeOH/KOH/H_2O (4 mL, mass ratio: 4:2:2) and stirred for 1 h at room temperature. Then the organic layer was washed three times with water and after drying over anhydrous sodium sulfate was distilled under a vacuum of 20 mmHg. Yellowish liquids **1a–k** were obtained.

2-Methyl-3-phenylpropanal (**1a**): Oil; ^{1}H NMR δ 9.65 (1H, s, CHO), 7.31–7.05 (5H, m, ArH), 3.08–3.03 (1H, dd, *J* = 5.6, 13.2 Hz, CH_{2a}), 2.66–2.54 (2H, m, CH_{2b}, CH), 1.05 (3H, d, *J* = 8.0 Hz, CH_3); ^{13}C NMR δ 203.9, 138.6, 128.8, 128.3, 126.2, 48.0, 36.7, 13.3; MS (ESI): *m/z* = 147[M-H]$^-$.

*2-Methyl-3-(*p*-tolyl)propanal* (**1b**): Oil; ^{1}H NMR δ 9.65 (1H, s, CHO), 7.12–7.00 (4H, m, ArH), 3.03–2.98 (1H, dd, *J* = 4.0, 12.0 Hz, CH_{2a}), 2.65–2.50 (2H, m, CH_{2b}, CH), 2.29 (3H, s, CH_3), 1.05 (3H, d, *J* = 8.0 Hz, CH_3); ^{13}C NMR δ 204.3, 141.8, 137.8, 129.4, 127.8, 39.7, 28.9, 16.0, 14.1; MS (EI): *m/z* =162 [M].

3-(4-Ethylphenyl)-2-methylpropanal (**1c**): Oil; ^{1}H NMR δ 9.66 (1H, s, CHO), 7.16 – 7.04 (4H, m, ArH), 3.04 – 3.00 (1H, dd, *J* = 8.0, 16.0 Hz, CH_{2a}), 2.66 – 2.52 (4H, m, CH_{2b}, CH_2, CH), 1.21 (3H, t, *J* = 8.0 Hz, CH_3), 1.06 (3H, d, *J* = 8.0 Hz, CH_3); ^{13}C NMR δ 204.1, 137.5, 135.3, 129.3, 129.0, 39.7, 37.3, 21.4, 14.0; MS (EI): *m/z* =175 [M-H]$^-$.

3-(4-Isopropylphenyl)-2-methylpropanal (**1d**): Oil; ^{1}H NMR δ 9.67 (1H, s, CHO), 7.13 (2H, d, *J* = 8.0 Hz, ArH), 7.06 (2H, d, *J* = 8.0 Hz, ArH), 3.06–3.01 (1H, dd, *J* = 8.0, 16 Hz, CH_{2a}), 2.91 – 2.81 (H, m, CH), 2.65 – 2.53 (2H, m, CH_{2b}, CH), 1.23 (6H, d, *J* = 4.0 Hz, CH_3), 1.07 (3H, d, *J* = 8.0 Hz, CH_3); ^{13}C NMR δ 204.0, 129.1, 128.8, 128.5, 45.1, 36.4, 30.3, 22.5, 13.3; MS (EI): *m/z* = 190 [M].

3-(4-(t-Butyl)phenyl)-2-methylpropanal (**1e**): Oil; ^{1}H NMR δ 9.65 (1H, s, CHO), 7.27 (2H, d, *J* = 8.0 Hz, ArH), 7.06 (2H, d, *J* = 8.0 Hz, ArH), 3.04–2.99 (1H, dd, *J* = 5.6, 13.2 Hz, CH_{2a}), 2.66–2.51 (2H, m, CH_{2b}, CH), 1.29 (9H, s, CH_3), 1.05 (3H, d, *J* = 8.0 Hz, CH_3); ^{13}C NMR δ 204.3, 148.5, 137.4, 128.8, 125.1, 39.3, 37.1, 37.0, 34.4, 31.5, 13.9; MS (ESI): *m/z* =227 [M+Na]$^+$.

3-(4-(sec-Butyl)phenyl)-2-methylpropanal (**1f**): Oil; ^{1}H NMR δ 9.69 (1H, s, CHO), 7.13 (2H, d, *J* = 8.0 Hz, ArH), 7.06 (2H, d, *J* = 8.0 Hz, ArH), 3.07 – 3.02 (1H, dd, *J* = 8.0, 12.0 Hz, CH_{2a}), 2.68 – 2.54 (2H, m, CH_{2b}, CH), 2.43 (H, d, *J* = 8.0 Hz, CH_2), 1.88 – 1.78 (1H, m, CH), 1.08 (3H, d, *J* = 8.0 Hz, CH_3), 0.89 (6H, d, *J* = 8.0 Hz, CH_3); ^{13}C NMR δ 204.1, 129.1, 128.8, 128.5, 48.1, 45.1, 36.4, 30.3, 22.5, 13.3; MS (ESI): *m/z* =227 [M+Na]$^+$.

3-4-Amyl-2-methyl-3-phenyl propanal (**1g**): Oil; ^{1}H NMR δ 9.70 (1H, s, CHO), 7.27 (2H, d, *J* = 8.0 Hz, ArH), 7.06 (2H, d, *J* = 8.0 Hz, ArH), 3.06 – 3.02 (1H, dd, *J* = 4.0, 12.0 Hz, CH_{2a}), 2.70 – 2.54 (2H, m, CH_{2b}, CH), 2.45 – 2.35 (2H, m, CH_2), 1.28 (6H, s, CH_3), 1.08 (3H, d, *J* = 8.0 Hz, CH_3), 0.66 (3H, t, *J* = 8.0 Hz, CH_3). ^{13}C NMR δ 204.1, 147.3, 135.3, 128.4, 125.9, 48.0, 37.6, 36.9, 36.2, 28.5, 13.4, 9.2; MS (ESI): *m/z* =217 [M-H]$^-$.

3-(4-Methoxyphenyl)-2-methylpropanal (**1h**): Oil; ^{1}H NMR δ 9.67 (1H, s, CHO), 7.05 (2H, d, *J* = 8.0 Hz, ArH), 6.81 (2H, d, *J* = 8.0 Hz, ArH), 3.76 (3H, s, CH_3), 3.02 – 2.98 (1H, dd, *J* = 4.0, 12.0 Hz, CH_{2a}), 2.64 – 2.52 (2H, m, CH_{2b}, CH), 1.06 (3H, d, *J* = 8.0 Hz, CH_3); ^{13}C NMR δ 204.1, 157.5, 130.0, 113.5, 55.1, 39.5, 36.5, 13.7; MS (ESI): *m/z* = 201 [M+Na]$^+$.

We thank Zhejiang University of Technology (ZJUT) for financial support.

Received 29 July 2015; accepted 21 August 2015
Paper 1503515 doi: 10.3184/174751915X14408762827272
Published online: 2 October 2015

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