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Indanones and Indenols from 2-Alkylcinnamaldehydes via the Intramolecular Friedel−Crafts Reaction of Geminal Diacetates

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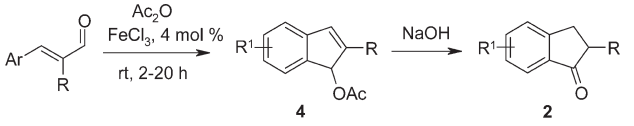

4 2

When treated with Ac_2O at rt in the presence of 4−6 mol % $FeCl_3$, 2-alkylcinnamaldehydes are converted to 2-alkyl-1*H*-inden-1-yl acetates through the intermediacy of *gem*-diacetates. Methanolysis of the indenyl acetates yields the corresponding indenols. Saponification yields 2-alkylindanones, providing, in effect, an intramolecular acylation employing catalytic levels of acid.

Geminal dicarboxylates, or acylals, are prepared by the acid-catalyzed reaction between aldehydes and noncyclic anhydrides of carboxylic acids. The reaction is easily accomplished under mild conditions using a variety of Brønsted or Lewis acid catalysts.[1,2] A convenient, solventless procedure is to treat aldehydes with excess acetic anhydride and catalytic quantities of $FeCl_3$ at 0 °C.[3] Acylals have been proposed as aldehyde protecting groups.[2,4] Other synthetic uses are concerned mainly with substitution reactions of a carboxylate group with carbon nucleophiles.[1,5] Acetic acid elimination from the diacetate acylals of α,β-unsaturated aldehydes produces 1-acetoxy-1,3-dienes, which have been used in Diels−Alder reactions.[6] Acylals of α,β-unsaturated aldehydes also have been employed as substrates in Pd-catalyzed allylic substitutions.[7] In the presence of Lewis acids, the acylals of acrolein and 2-alkylacroleins will alkylate aromatic rings, yielding the enol acetates of 3-arylpropanals, the Scriabine reaction.[8] This reaction, which provides a route to 3-arylpropanals, was described by Igor Scriabine in 1961. The transformation was effected by treating the unsaturated acylals with an excess of arene and 1 equiv of $TiCl_4$ in combination with $BF_3 \cdot Et_2O$. More recent procedures developed for industrial purposes accomplish the reaction using substoichiometric levels of Lewis acid.[8e,8f]

Recently, we reported that in situ generated dimethyl acetals of (*E*)-2-alkylcinnamaldehydes cyclize in the presence of catalytic quantities of $FeCl_3$, yielding 1-alkoxy-2-alkyl-1*H*-indenes (**1**).[9,10] Typically, indene formation was effected using 5−10 mol % $FeCl_3$ in refluxing MeOAc. These indenes were then transformed in two steps (base-catalyzed double-bond migration to form the enol ether and acid-catalyzed hydrolysis) into 2-alkylindanones (**2**). Formally, the transformation corresponds to an intramolecular Friedel−Crafts acylation achieved with catalytic quantities of Lewis acid.[11] Traditional Friedel−Crafts acylations require stoichiometric amounts of Lewis acid to proceed to completion because of coordination of Lewis acid with the resulting aryl ketones. On the basis of the precedents of our acetal cyclization and the Scriabine reaction, it seemed plausible that

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(10) The formation of **1** has also been reported using a stoichiometric amount of $BF_3 \cdot Et_2O$: (a) Jobashi, T.; Kawai, A.; Kawai, S.; Maeyama, K.; Oike, H.; Yoshida, Y.; Yonezawa, N. *Tetrahedron* **2006**, *62*, 5717–5724. (b) Jobashi, T.; Maeyama, K.; Noguchi, K.; Yoshida, Y.; Yonezawa, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 627–633.

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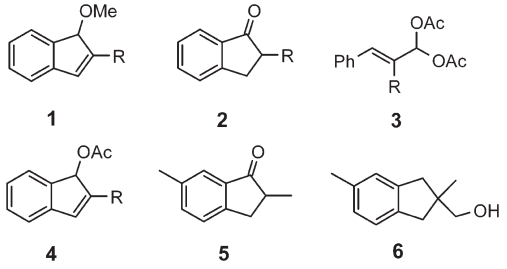
acylals of cinnamaldehydes (**3**) also would undergo an intramolecular Friedel−Crafts reaction to yield 2-alkyl-1*H*-inden-1-yl acetates (**4**) and that saponification of **4** would lead directly to **2**. Of particular interest to us was the potential of such a methodology for developing an industrial synthesis of 2,6-dimethylindan-1-one (**5**), which can be used to make 2,5-dimethyl-2-indanmethanol (**6**), a perfumery compound with a powerful lily-of-the-valley, floral-type odor.[12] Previous approaches to **5** required either heating of the requisite 3-arylcarboxylic acid in polyphosphoric acid[13] or treatment of the corresponding acid chloride with 1 equiv of $AlCl_3$.[14]

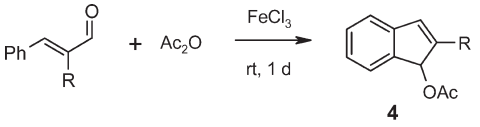


Both Pinnick et al.[3] and Trost et al.[7a,7b] reported the preparation of the diacetate acylal of (*E*)-cinnamaldehyde by treatment of the enal with an excess of acetic acid anhydride and a catalytic quantity of $FeCl_3$ at 0 °C. We also observed acylal formation when we treated cinnamaldehyde with excess acetic anhydride and 4 mol % of $FeCl_3$ at rt or 75 °C. GC−MS analysis showed no evidence for the formation of an indene product in either case. Polymerization to higher molecular weight materials occurred in both reaction mixtures, and after just a few hours at 75 °C, all of the enal and acylal were consumed. However, when we treated (*E*)-2-methylcinnamaldehyde with 1.5 equiv of acetic anhydride and 4 mol % of $FeCl_3$ at rt, the anticipated indenyl acetate product (**4a**) was formed. GC analysis of the reaction mixture after 3 h showed the presence of both **4a** and the acylal in about equivalent amounts. After 1 day of stirring, **4a** was the major product and was isolated in 36% yield (Table 1, entry 1). In contrast, the (*E*)-2-alkylcinnamaldehydes with larger alkyl groups reacted more efficiently to form the indenyl acetates in yields of 78−84% with complete consumption of the starting enals (entries 2−7). A 1-day reaction period is not necessary because **4e** was isolated in 88% yield after a 2-h reaction period (entry 5). For 2-methylcinnamaldehyde, increasing the level of acetic anhydride to 3 equiv and the catalyst level to 6 mol % resulted in the complete consumption of the enal and acylal but only modestly improved the yield of **4a** to 48% (entry 1).

Identification of the acylal in the **4a** reaction mixture indicated that indenyl acetates were formed by cyclization of an initially formed acylal intermediate. However, another possible pathway was that 2-alkylcinnamaldehydes cyclized to indenol intermediates, which then were acetylated under the reaction conditions. The acid-catalyzed cyclization of some 3-aryl-2-alkyl-2-propenals into 2-alkylindenols has been reported but only in cases where the aryl ring bore electron-donating groups.[15] We found no evidence for indenol intermediates in our reaction mixtures, and no indene products were observed in the absence of acetic anhydride. In the case of 2-hexylcinnamaldehyde, treating the enal with less catalyst (1 mol %) at 0 °C allowed the preparation of the acylal (**3g**). However, even under these conditions, cyclization to **4g** occurred, so the reaction mixture was worked up after just 30 min to afford **3g** in 59% yield (*E*/*Z* = 85:15). When a CH_2Cl_2 solution of **3g** was treated with 4 mol % $FeCl_3$ at rt, the acylal was completely consumed within 1 h and **4g** was isolated in 87% yield.

On the basis of these results, we propose an intramolecular Friedel−Crafts reaction in which an allylic oxocarbenium ion, derived from the in situ generated acylal, alkylates the phenyl group to form the indane skeleton (Scheme 1). This process is analogous to that proposed for cyclization of the dimethyl acetals of 2-alkylcinnamaldehydes.[9,10] In order for cyclization to occur, the stereochemical integrity of the enal *E*-configured double bond must be lost. While this requirement was recognized previously in the case of acetal cyclization, a pathway to account for it was not proposed. A potential mechanism would be an allylic rearrangement of the acylal to a 1,3-diacetoxy-1-propene intermediate **7** (Scheme 1). This intermediate could regenerate either the

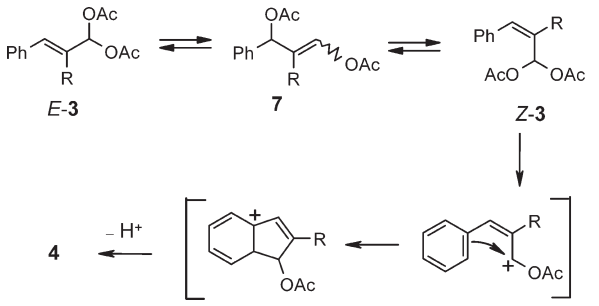
TABLE 1. Preparation of 4a−g[a]



entry	R	enal (*E*/*Z*)	product	isolated yield (%)
1	Me	100:0	**4a**	36, 48[b]
2	Et	96:4	**4b**	79, 84[b]
3	Pr	96:4	**4c**	78
4	^{i}Pr	60:40	**4d**	82
5	Bu	95:5	**4e**	83, 88[c]
6	pentyl	92:8	**4f**	84
7	hexyl	91:9	**4g**	80, 82[d]

[a]Reaction conditions: 1.5 equiv of Ac_2O, 4 mol % $FeCl_3$, rt, 1 day. [b]Reaction conditions: 3 equiv of Ac_2O, 6 mol % $FeCl_3$. [c]Reaction conditions: 2 h at rt. [d]Reaction conditions: 3 equiv of Ac_2O, 2 h at rt.

SCHEME 1. Mechanism for the Formation of 4



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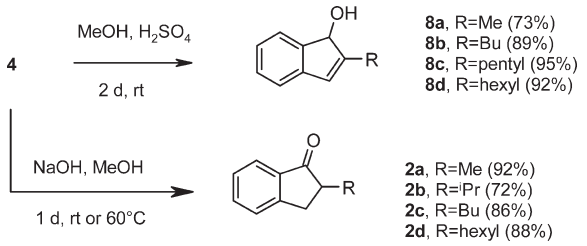
SCHEME 2. Preparation of 2 and 8



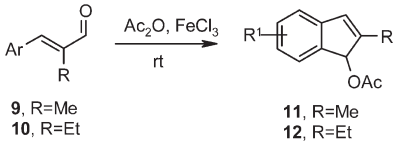
E- or *Z*-acylal, resulting in isomerization of the double bond, or it could lead directly to the cationic species needed for the intramolecular Friedel−Crafts reaction. While we did not observe intermediate **7**, the generation of 1,3-diacetoxy-1-propenes from diacetate acylals of α,*β*-unsaturated aldehydes is known.[16] These compounds also were noted as minor byproducts in the $FeCl_3$-catalyzed preparation of the diacetate acylals of 2-hexenal and crotonaldehyde.[7a]

The only previously known member of the **4** series is **4a**. It was prepared in a five-step process involving conversion of benzaldehyde to 2-methylindenone, $NaBH_4/CeCl_3$ reduction to 2-methyl-1-indenol (**8a**), followed by acetylation.[17] Our new method for the direct conversion of 2-alkylcinnamaldehydes to **4** is a much more convenient and direct route. Convenient routes to 2-alkylindenols **8** and 2-alkylindanones **2** were realized by the acid-catalyzed methanolysis or saponification of **4**, respectively (Scheme 2).

Indenols **8a**−**d** were isolated in good yields after treating **4** with methanol and H_2SO_4 at rt. All proved to be solids, but only **8a** could be recrystallized. Base-catalyzed hydrolysis of **4** was expected to yield **2** via the initial formation of **8**, followed by double-bond migration to the enol. The base-catalyzed conversion of indenols to indanones is known,[18] and the migration of the indenyl double bond is believed to proceed by a series of suprafacial 1,5-H shifts.[19] Treatment of **4g** with methanolic NaOH (3 equiv) at rt resulted in the complete consumption of indenyl acetate within 5 h and the formation of two products. From this mixture, **8d** and **2d** were isolated in 62% and 36% yields, respectively. Indanone was obtained in 88% yield as the only product after heating the reaction mixture at 60 °C for 1 day. Indanones **2a**−**c** were isolated in yields of 72−92% after being treated with 3 equiv of NaOH at rt for 24 h.

Interested in a route to indanone **5**, we prepared indenyl acetates from 3-aryl-2-methylpropenals **9** and 3-aryl-2-ethylpropenals **10** with substituents on the aromatic ring (Table 2). The enals were treated with 3 equiv of Ac_2O and 4−6 mol % $FeCl_3$ at rt. As was found for the simple 2-alkylcinnamaldehydes (Table 1), the 2-methylenals **9** required a 1-day reaction period to completely consume the starting enal and afforded only moderate yields (42−49%) of indenyl acetates (entries 1−3), while the corresponding 2-ethylenals **10** were consumed within 2−8 h and resulted in indenyl acetate yields of 82−89% (entries 5−7). A *p*-methoxy group on the aryl ring resulted in significant decomposition and subsequently low yields of the cyclized products (entries 4 and 8). In the case of the 2-methylenal **9d**, GC−MS analysis of the reaction mixture indicated only a low level of the expected indenyl acetate **11d** and incomplete consumption of the starting enal and acylal intermediate. Bulb-to-bulb distillation of this reaction mixture showed that the experiment yielded mostly a polymeric residue. Cyclization of the ethyl analogue **10d** was more efficient, but the catalyst level was increased to 6% and the mixture stirred for 8 h to ensure consumption of the starting enal. **12d** was isolated in only 25% yield, with the reaction producing mostly a polymeric residue. For 2-ethyl-*p*-chlorocinnamaldehyde, the reaction proceeded normally (6 mol % $FeCl_3$ used) to yield **12e** in 82% yield (entry 9).

TABLE 2. Indenyl Acetates with Substituents on the Aromatic Ring[a]



entry	aryl group	R	enal	product	isolated yield (%)
1	4-MeC_6H_4	Me	**9a**	**11a**	49
2	2-MeC_6H_4	Me	**9b**	**11b**	44
3	4-$^tBuC_6H_4$	Me	**9c**	**11c**	42
4	4-$MeOC_6H_4$	Me	**9d**	**11d**	0[b]
5	4-MeC_6H_4	Et	**10a**	**12a**	82
6	2-MeC_6H_4	Et	**10b**	**12b**	82
7	4-$^tBuC_6H_4$	Et	**10c**	**12c**	89
8	4-$MeOC_6H_4$	Et	**10d**	**12d**	25[c]
9	4-ClC_6H_4	Et	**10e**	**12e**	82

[a]Reaction conditions: 3 equiv of Ac_2O, 4−6 mol % $FeCl_3$, no solvent, rt, 1 day (R = Me), 2−6 h (R = Et). [b]Trace level of **11d** detected by GC−MS analysis. [c]Reaction conditions: 6 mol % $FeCl_3$, rt, 8 h.

Treatment of **11a** with NaOH (rt, 1 day) yielded **5** in 81% yield, the structure of which was confirmed by a comparison with the literature NMR data for both **5** and 2,5-dimethylindanone.[13] The exclusive formation of **5** proves that cyclization of the acylal proceeded without scrambling of the acetate group between C(1) and C(3) of the resulting indene.

Because **11a** was formed in only 49% yield, the overall isolated yield of **5** from **9a** was just 40%. Therefore, we sought to improve the yield of the cyclization reaction. Other acids ($SnCl_4$, $BF_3\cdot Et_2O$, $ZnCl_2$, $AlCl_3$, $EtAlCl_2$, $TiCl_4$, and H_2SO_4) were screened using our typical conditions (Table 2) while monitoring the product yield by GC analysis with dodecane as an internal standard. While $SnCl_4$ and $BF_3\cdot Et_2O$ were comparable to $FeCl_3$, none of the tested catalysts proved superior. While we remained focused on $FeCl_3$, other reaction parameters were varied using the readily available 2-methylcinnamaldehyde as the substrate. Conditions were developed that improved the isolated yield of **4a** from 48% (Table 1, entry 1) to 75% while reducing the catalyst level from 6 mol % to just 0.5 mol %. This was achieved by heating the enal/acetic anhydride (4 equiv) reaction mixture at 116 °C for 30 min while adding the catalyst (0.5 mol % $FeCl_3\cdot 6H_2O$ in 1 equiv of acetic anhydride) dropwise. Conversion of **4a** to **2a** in 92% yield (Scheme 2) resulted in an overall 69% yield of **2a** from 2-methylcinnamaldehyde.

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Applying the same cyclization conditions to **9a** improved the yield of **11a** from 49% to 68% for an overall yield of 55% **5** from the enal.

In conclusion, we have found that the in situ generated acylals of 2-alkylcinnamaldehydes undergo an intramolecular Friedel−Crafts reaction to yield indenyl acetates at rt in the presence of catalytic amounts of $FeCl_3$ (4−6 mol %). Yields from 2-methylcinnamaldehydes were moderate (36−49%), while those from the corresponding 2-ethylcinnamaldehydes were good (82−89%). In the case of 2-methylcinnamaldehyde, the yield of **4a** was improved to 75% and the catalyst level reduced to just 0.5 mol % by heating the reaction mixture (116 °C) for 30 min while adding the catalyst dropwise. Saponification of the indenyl acetates afforded 2-alkylindanones in high yields. The net effect of these two steps is acylation of the aryl ring using catalytic quantities of the Lewis acid. In contrast, a traditional Friedel−Crafts acylation route to 1-indanones requires at least a stoichiometric level of the acid promoter.[20]

Experimental Section

General Procedure for the Preparation of Indenyl Acetates. A mixture of 2-alkylcinnamaldehyde aldehyde (50 mmol) and acetic anhydride (75−150 mmol) was cooled in an ice bath. Anhydrous $FeCl_3$ (0.3 g, 1.8 mmol) was added and the mixture stirred for 15 min. The reaction mixture was removed from the cold bath and stirred on the bench for 2−24 h. It was then diluted with 100 mL of diethyl ether and washed with water (2 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The products were isolated directly by bulb-to-bulb distillation to yield acetates as pale-yellow liquids. In a few cases, the distillates were further purified by flash chromatography (hexane/EtOAc).

2-Methyl-1*H*-inden-1-yl Acetate (4a). A mixture of 2-methylcinnamaldehyde (2.92 g, 20 mmol), acetic anhydride (6.1 g, 60 mmol), and $FeCl_3$ (0.2 g, 1.2 mmol) was stirred at rt for 1 day. After workup, bulb-to-bulb distillation (140 °C, 0.025 mmHg) afforded 1.8 g (9.6 mmol, 48% yield) of **4a** as a yellow oil. NMR data matched that reported in the literature:[17] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.97 (s, 3H), 2.17 (s, 3H), 6.14 (s, 1H), 6.41 (s, 1H), 7.07 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 7.4 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.35 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 21.0 (q), 78.4 (d), 120.3 (d), 124.2 (d), 125.1 (d), 128.8 (d), 129.3 (d), 142.1 (s), 143.7 (s), 144.4 (s), 171.5 (s).

General Procedure for the Preparation of 2-Alkylindenols. In a typical procedure, 39 mmol of 2-alkyl-1*H*-inden-1-yl acetate was mixed with 50 mL of methanol and 0.7 g (7 mmol) of concentrated H_2SO_4. The mixture was stirred for 2 days at room temperature and then neutralized with 1 g of Na_2CO_3. The mixture was filtered and concentrated under vacuum. The residue was subjected to bulb-to-bulb distillation or flash chromatography (95:5 hexane/ethyl acetate) to yield **8** as a pale-yellow solid.

2-Methyl-1*H*-inden-1-ol (8a). From 3.0 g (16 mmol) of **4a**, 1.7 g (11.6 mmol, 73% yield) of **8a** was isolated by bulb-to-bulb distillation (120 °C, 0.03 mmHg) as a pale-yellow solid. Recrystallization from pentane/EtOAc afforded white crystals; mp = 83−85 °C (lit.[17] mp 84−86 °C). NMR data matched that reported in the literature:[17] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (s, 3H), 2.10 (s, 1H), 4.72 (s, 1H), 6.27 (s, 1H), 7.04−7.19 (m, 3H), 7.36 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (q), 78.7 (d), 120.0 (d), 123.3 (d), 124.8 (d), 126.8 (d), 128.4 (d), 143.0 (s), 145.2 (s), 148.4 (s).

General Procedure for the Preparation of 2-Alkylindanones. In a typical procedure, 20 mmol of indenyl acetate was mixed with 30 mL of MeOH and 20 mL of 3 M NaOH. In the case of **4a**, **4d**, **4e**, and **9a**, the mixtures were stirred at rt for 1 day. For **4g**, the reaction mixture was heated at 60 °C for 1 day. After neutralization with 21 mL of 1.5 M H_2SO_4 and dilution with 100 mL of water, the mixture was extracted with diethyl ether. The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to bulb-to-bulb distillation or flash chromatography (98:2 hexane/ethyl acetate) to yield indanones **2** and **5**.

2-Methylindanone (2a). A mixture of **4a** (21.3 mmol), MeOH (25 mL), and 3 M NaOH (22 mL) was stirred for 1 day and then neutralized with 1.5 M H_2SO_4 (23.1 mL). After workup, bulb-to-bulb distillation afforded 2.85 g (19.5 mmol, 92% yield) of **2a** as a pale-yellow oil. NMR data matched that reported in the literature:[21] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, J = 7.4 Hz, 3H), 2.66−2.74 (m, 2H), 3.39 (dd, J = 8.2 and 17.4 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.57 (dt, J = 7.5 and 1.1 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (q), 34.9 (t), 42.0 (d), 123.9 (d), 126.6 (d), 127.3 (d), 134.7 (d), 136.3 (s), 153.5 (s), 209.4 (s).

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Supporting Information Available: Details of the alternate, reduced-catalyst experimental procedure for preparing **4a** and **11a**, procedure for preparing **3g**, and compound characterization data and copies of the ^{1}H and ^{13}C NMR spectra for compounds **2**, **3g**, **4**, **8**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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