Superacidic trifluoromethanesulfonic acid-induced cycli-acyalkylation of aromatics

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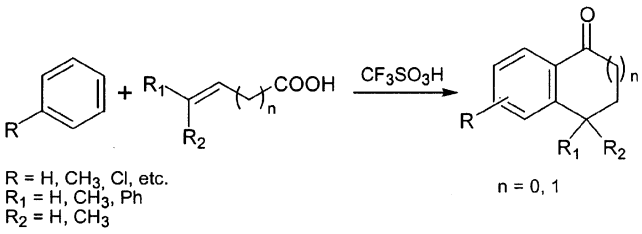
Superacidic trifluoromethanesulfonic acid-induced synthesis of 1-indanone and 1-tetralone derivatives through Friedel–Crafts cycli-acyalkylation of aromatics with unsaturated carboxylic acids was achieved. Depending on the reactant used, different substituted indanones and tetralones were obtained in moderate to good yields.

KEY WORDS: Friedel–Crafts cycli-acyalkylation; trifluoromethanesulfonic acid; superelectrophilic activation; indanone; tetralone.

1. Introduction

Friedel–Crafts acylation and alkylation are important methodologies for carbon–carbon bond formation with aromatic compounds [1]. Friedel–Crafts cyclization reactions [2,3], either of an intramolecular or intermolecular nature, can lead to a variety of useful carbocyclic compounds, such as quinolines [2a], lactones [2b], condensed aromatics [2c], and cyclic aromatic ketones [1a,3]. Many of these cyclizations involve a single aromatic substrate through a facile intramolecular pathway by taking advantage of the close spatial arrangement of the two reacting centers. In contrast, bimolecular Friedel–Crafts cyclizations, in which bifunctional electrophiles react intramolecularly with the same aromatic ring, are more difficult to carry out and competitive intermolecular reactions will significantly decrease the possibility of cyclization. A bifunctional substrate capable of both acylation and alkylation of aromatic compounds is appealing for the formation of useful cyclic aromatic ketones. Among them, the five- and six-membered ring products indanones and tetralones belong to an important class of compounds and are frequently used as precursors in the synthesis of pharmaceuticals and natural products [4]. Particularly, 6-aryltetralones are important intermediates for the preparation of CNS agents. Extensive efforts have been devoted to develop new synthetic methodologies for indanone and tetralone derivatives [5]. Friedel–Crafts-type cycli-acyalkylation was investigated previously using aluminum chloride [3a–c] and polyphosphoric acid (PPA) [3d]. However, these methods usually resulted in low yields and were only occasionally applied.

We report a new general synthesis of 1-indanone and 1-tetralone derivatives through superacid-catalyzed cycli-acyalkylation of aromatics with alkenyl carboxylic acids and acid derivatives (scheme 1). Trifluoromethanesulfonic acid (triflic acid) was found to be an excellent catalyst/medium for cycli-acyalkylation. The reaction allows the preparation of substituted 1-indanones and 1-tetralones in a one-pot reaction.



Scheme 1.

2. Experimental

Triflic acid was freshly distilled prior to use. In a dry reaction flask, arenes (1 mmol) and unsaturated acid (1 mmol) were dissolved in 0.5 ml of dry CH_2Cl_2 or $ClCH_2CH_2Cl$. Subsequently, 1 ml of triflic acid (~5 equiv.) was slowly added to the stirred solution at 0 °C and the mixture was heated to the desired temperature and allowed to react for a given period of time. The solution was then poured onto ice and extracted with CH_2Cl_2. After evaporation of solvents, the crude product was purified by flash chromatography and analyzed by GC-MS and NMR.

New compounds were characterized by NMR (^1H, ^{13}C) spectroscopy using Bruker AC-250 or AM-360 spectrometers. The spectra were recorded in $CDCl_3$ using TMS as internal standard.

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4,7-Dimethyl-3-phenyl-indan-1-one: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.86 (s, 3H), 2.46 (dd, $J = 2.6$, 18.7 Hz, 1H), 2.57 (s, 3H), 3.09 (dd, $J = 8.7$, 18.7 Hz, 1H), 4.40 (dd, 1H), 6.88–7.21 (m, 7H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 17.8, 17.9, 43.0, 47.8, 126.3, 127.1, 128.6, 129.9, 133.5, 134.2, 156.0, 143.8, 135.5, 135.5, 207.2.

4,6-Dimethyl-3-phenyl-indan-1-one: ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.97 (s, 3H), 2.39 (s, 3H), 2.58 (dd, $J = 3.0$, 19.6 Hz, 1H), 3.22 (dd, $J = 7.9$, 19.6 Hz, 1H), 4.53 (br d, $J = 7.9$ Hz, 1H), 7.02 (m, 2H), 7.25 (m, 4H), 7.48 (s, 1H). ^{13}C NMR (63 MHz, $CDCl_3$): δ 18.2, 21.0, 43.5, 47.9, 120.9, 126.6, 127.3, 128.8, 136.4, 137.4, 137.7, 138.3, 143.9, 153.2, 206.8.

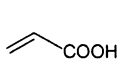
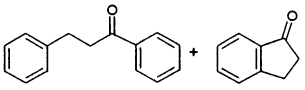
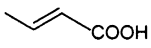
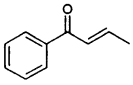
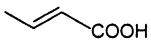
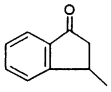
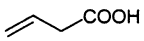
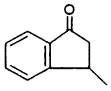
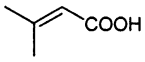
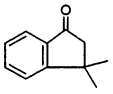
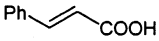
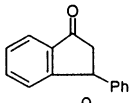
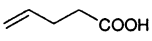
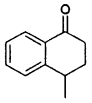
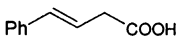
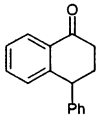
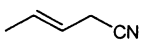
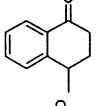
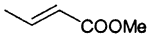
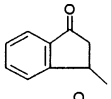
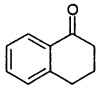
4,7-Dichloro-3-phenyl-indan-1-one: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (br d, $J = 19.0$ Hz, 1H), 3.27 (dd, $J = 8.2$, 19.4 Hz, 1H), 5.04 (br s, 1H), 6.81–7.83 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.00, 45.0, 123.8, 126.7, 128.3, 128.4, 130.9, 132.2, 133.1, 135.3, 137.2, 155.5, 204.7.

5,8-Dimethyl-4-phenyl-tetral-1-one: ^{1}H NMR (360 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.23 (m, 1H), 2.38–2.62 (m, 3H), 2.68 (s, 3H), 4.47 (m, 1H), 6.95–7.40 (m, 7H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 19.5, 23.5, 30.3, 35.2, 41.7, 126.4, 128.2, 128.4, 130.9, 132.0, 134.4, 134.7, 139.0, 141.8, 144.3, 200.6.

3. Results and discussion

Initially, benzene was used as the aromatic substrate to react with a variety of unsaturated carboxylic acids and their derivatives in the presence of triflic acid. The results are shown in table 1.

Table 1
Triflic acid-catalyzed preparation of substituted indanones and tetralones by cycli-acylalkylation of benzene with unsaturated carboxylic acids and derivatives

Entry	Electrophile	Temperature (°C)	Time (h)	Product	Yield [a] (%)
1		20	16		41 + 6
2		20	20		21
3		80	20		80
4		20	20		77
5		80	20		83
6		80	16		86
7		80	20		85
8		20	18		72
9		80	20		22
10		80	20		45
11		80	24		11

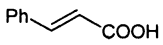
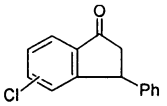
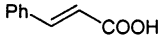
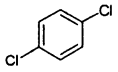
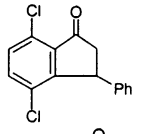
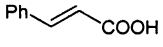
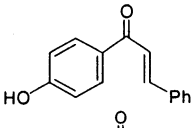
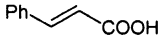
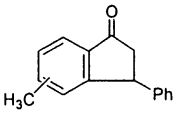
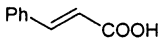
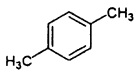
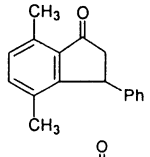
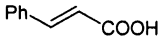
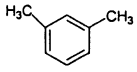
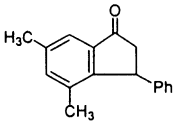
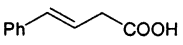
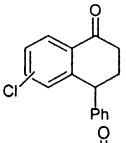
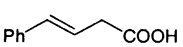
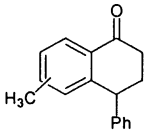
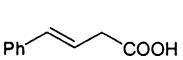
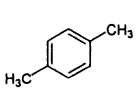
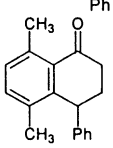
[a] Isolated yield.

In the case of acrylic acid (table 1, entry 1), both diphenylated linear product and cyclized 1-indanone were obtained with the intermolecular reaction product dominating. Attempts to increase the ratio of cyclized product by using higher equivalents of acrylic acid had no effect on the selectivity but decreased the overall yield significantly. Using more reactive toluene instead of benzene slightly increased the selectivity of cyclization and gave the linear product and cyclized product in 23% and 28% yield, respectively. The low selectivity of cyclic product formation is due to the lack of significant reactivity difference between the C=C double bond and the carboxylic acid functionality. As can be seen from entries 3–6 in table 1, with increasing stability of the carbocation formed from the alkene, the yield of the cyclic indanone product increased accordingly. Following the same trend, we were able to obtain the six-membered ring tetralone from 4-pentenoic acid (entry 7) and styrylacetic acid (entry 8) in good yields.

Besides alkenyl carboxylic acids, alkenyl nitrile (entry 9), alkenyl ester (entry 10), and lactone (entry 11) were also tested in the cyclization reaction and the expected cyclic products were obtained in moderate yields. These functional groups can be viewed as protected carboxylic acid functions and they are not as reactive as the acid functions; however, in superacidic media they also underwent cyclization.

Based on the results of the reactions of benzene and toluene, a wide range of aromatics were reacted with cinnamic acid and styrylacetic acid under similar

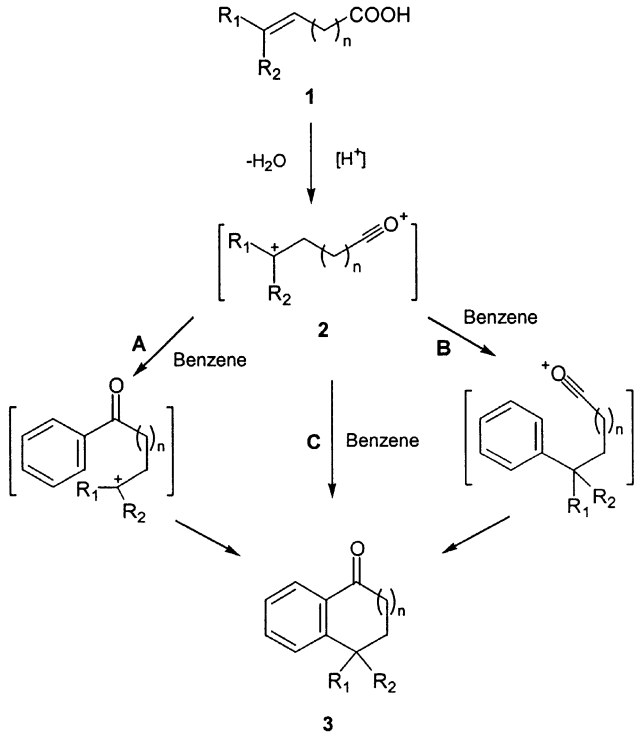
Table 2
Triflic acid-catalyzed preparation of phenyl-indanones and -tetralones through the reaction of cinnamic acid and styrylacetic acid with aromatics (20 h reaction time)

Entry	Electrophile	Temperature (°C)	Aromatic	Product	Yield (%)
1		20			93
2		80			50
3		50			77
4		80			78
5		80			95
6		20			85
7		20			6
8		20			80
9		20			82

reaction conditions giving the corresponding 3-phenyl-1-indanones and 4-phenyl-1-tetralones. The results are shown in table 2.

The observation of a significantly lower yield from the reaction of chlorobenzene with styrylacetic acid (entry 7) compared to cinnamic acid (entry 1), led us to examine the possibility of polymerization of these two unsaturated carboxylic acids in the absence of arenes. Upon reacting triflic acid with styrylacetic acid and cinnamic acid, respectively, in the absence of aromatics, styrylacetic acid indeed easily undergoes oligomerization in the presence of triflic acid whereas the conjugated cinnamic acid does not. When activated aromatics were used, both acids gave the cyclization products in good yield indicating the dominant role of cycli-acyalkylation compared to oligomerization. As the activity of the aromatics decreases (entries 1, 7), oligomerization of styrylacetic acid prevailed and gave the tetralone only in low yield. However, indanone was still obtained from cinnamic acid and chlorobenzene in good yield.

There are three possible mechanistic pathways for the formation of the cyclic product involving the super-electrophilic dication **2** [6], as shown in scheme 2. The first is initial acylation followed by alkylation (**A**), the second is initial alkylation followed by acylation (**B**), while the third is a concerted reaction path (**C**). The concerted cyclization is very unlikely under the extremely polar conditions. From the results shown in the cases of benzene–crotonic acid (table 1, entry 2) and phenol–styrylacetic acid (table 2, entry 3), only acylated products were formed with the complete absence of alkylated products. This can be explained by the deactivation of the aromatic ring upon initial acylation, which prevents further cycli-alkylation. Accordingly, we suggest that the reaction proceeds through initial intermolecular alkylation followed by an intramolecular cycli-acylation (pathway **B** in scheme 2).



Scheme 2.

4. Conclusion

Direct, one-flask syntheses of substituted 1-indanones and 1-tetralones were developed by superacid-catalyzed cycli-acyalkylation of aromatics with unsaturated carboxylic acid. As an extension of the Friedel–Crafts chemistry, the method can be applied to a variety of aromatics and unsaturated carboxylic acid derivatives involving a two-step intermolecular alkylation–intramolecular acylation mechanism.

Acknowledgment

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