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FRIEDEL-CRAFTS COORDINATED PROCESSES: HIGHLY SELECTIVE SYNTHESIS OF ETHYL-1-OXO-2-INDANCARBOXYLATES AND 1-OXO-2-ACETYLINDANES

Giovanni Sartori*[a], Franca Bigi[a], Xiaochun Tao[b], Giuseppe Casnati[a], Giacomo Canali[a]

[a] Istituto di Chimica Organica dell'Università, Viale delle Scienze, I-43100 Parma, Italy
[b] Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu,
Shanghai 200032, China

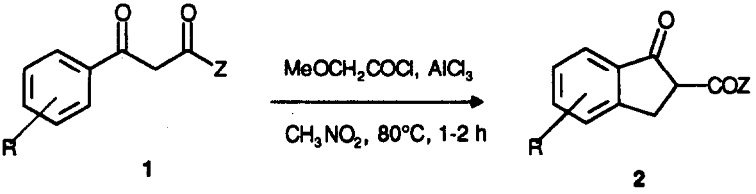
Key words: 1-oxo-indanes, chloromethylation, methoxymethylation.

Abstract: Alkyl 1-oxo-2-indancarboxylates and 1-oxo-2-acetylindanes were synthesized in good yields by methylenation of aromatic β-dicarbonyl compounds with $MeOCH_2COCl \cdot AlCl_3$ reagent.

Alkyl 1-oxo-2-indancarboxylates **2** (Z = OEt) and 1-oxo-2-acetylindanes **2** (Z = Me) are useful synthons for a great number of natural and biologically active compounds.[1]

The synthesis of products **2** by condensation of 1-oxo-indanes with alkyl carbonates under basic conditions is a well known process.[2] The precursory 1-oxo-indanes are obtained by cycliacylation of the corresponding 3-arylpropionic acid derivatives, whose preparation from aromatic aldehydes consists in a multistep synthesis.[3] While relatively simple the cycliacylation process requires either strong acidic media or the application of heat, often in excess of 150°C. A further limitation of this method is the migration of the alkyl groups and the ketone self-condensation under the condition of the reaction.[2,3]

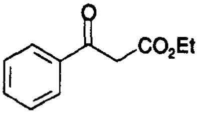
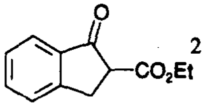
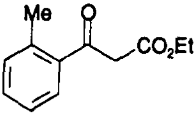
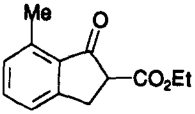
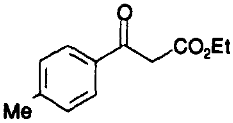
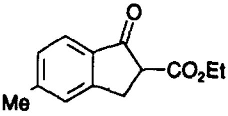
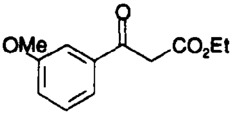
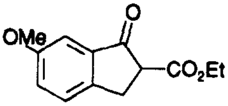
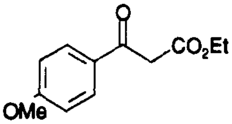
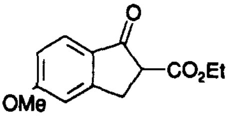
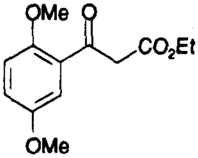
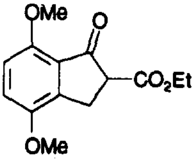
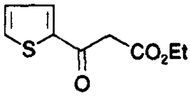
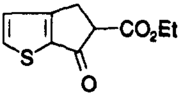
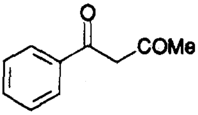
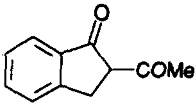
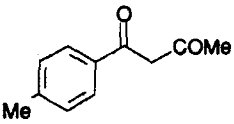
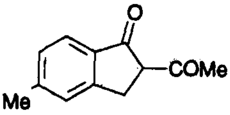
In the course of our investigation on the factors controlling the selectivity in the reaction of ambidental substrates with multireactive electrophiles,[4] we have found a new synthesis of the compounds **2** *via* C-selective bis-alkylation of the readily accessible β-dicarbonyl substrates **1** with the methoxyacetyl chloride-aluminum chloride reagent.



Z = OEt, Me ; R = H, Me, OMe

Scheme 1.

Electrophilic methylenation of aromatic β-dicarbonyl compounds (Scheme 1)

Entry	β-dicarbonyl[5] compound	Reaction Product*	Yield% (Selectivity%)
a		 [2]	60 (90)
b			68 (90)
c			62 (90)
d		 [2]	71 (91)
e		 [1]	70 (95)
f			40 (89)
g			62 (93)
h		 [6]	74 (94)
i			76 (93)

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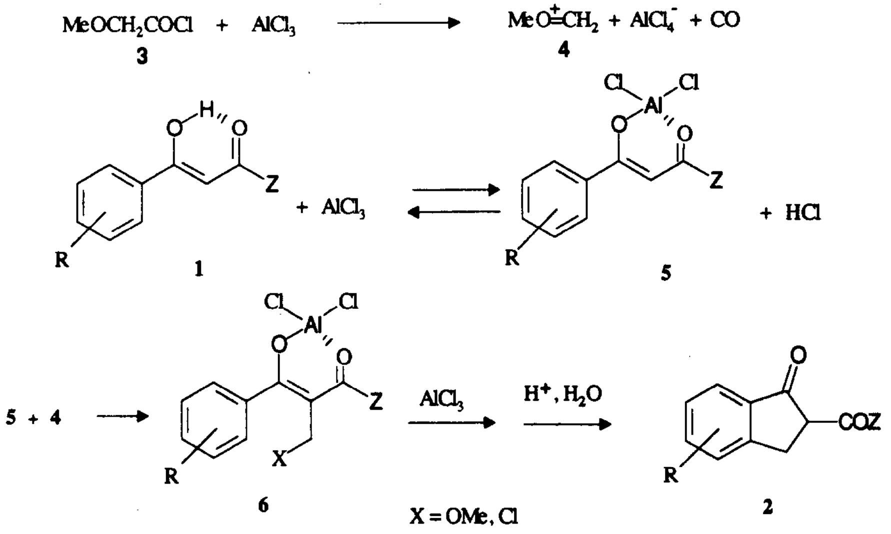
* Keto-enolic tautomerism is present.

We show here the synthetic application of such a methodology and some mechanistic speculations of the entire process.

The general procedure is illustrated as follows. Aluminum trichloride (1.33 g, 0.01 mol) and the β-dicarbonyl compound (0.005 mol) were dissolved in dry nitromethane (40 mL) under nitrogen. The mixture was stirred at room temperature for 15 minutes. Methoxyacetyl chloride (0.65 g, 0.006 mol) in dry nitromethane (10 mL) was added dropwise. After 15 minutes the reaction mixture was slowly heated at 80°C for 1-2 hours, then quenched with 10% aqueous oxalic acid and extracted with diethyl ether. After washing with 10% aqueous $NaHCO_3$ and drying with Na_2SO_4 the solvents were evaporated and the products were purified by flash chromatography (silica gel 60 mesh; eluent: hexane-ethyl acetate 5-20%).

We successfully applied this methodology to the synthesis of a wide series of ethyl-1-oxo-2-indancarboxylates and 1-oxo-2-acetylindanes. Satisfactory yields and good selectivities were observed in all cases. Synthetic results are reported in the Table.

On the basis of our previous results[4] and reports from literature[7] the complete reaction mechanism is regarded as shown in the Scheme 2.



Scheme 2.

Methoxyacetyl chloride 3 reacts with aluminum trichloride affording the methoxymethylene cation 4,[8] which undergo C-selective alkylation with the Al-chelate **5** producing the intermediate **6**.[9] Finally the aluminum trichloride-promoted cyclialkylation of **6** affords the product **2**.

The crucial role of the methoxymethylene carbonium ion **4** in the present methylenation process was demonstrated by carrying out the reaction with chloromethyl methyl ether which is easily converted into the reactive species **4** by treatment with Lewis acids.[10] Indeed the reaction of ethyl benzoylacetate

1a with chloromethyl methyl ether in the presence of aluminum trichloride afforded **2a** as the sole reaction product in 54% yield.

In summary, an efficient, highly selective method for the synthesis of alkyl 1-oxo-2-indancarboxylates and 1-oxo-2-acetylindanes by methylenation of convenient and readily accessible aromatic and heteroaromatic β-dicarbonyl compounds, has been developed. More extensive synthetic application and detailed mechanistic studies will be reported in due course.

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