Table I. Yields of Products from Acylation and Alkylation of Polymer-Bound Benzyl 3-Phenylpropanoate

polymer	RCOCl or RBr	product	% yield[a] 6 or 7	8	9
gel, 10% DVB[b]	p-$O_2NC_6H_4COCl$	6a	95 (85)	0	5
	CH_3COCl	6b	96 (87)	0	4
	n-C_4H_9Br	7a	97 (79)	0	2
	$C_6H_5CH_2Br$	7b	95 (73)	0	4
macroporous, 20% DVB[c]	p-$O_2NC_6H_4COCl$	6a	42 (40)	17	39
	CH_3COCl	6b	57	7	36
	n-C_4H_9Br	7a	63	1	36
	$C_6H_5CH_2Br$	7b	59	3	37

[a] Determined by GC from reactions using 5-10 g of polymer. Isolated yields from reactions using 25-50 g of polymer are in parentheses. [b] Polymer-bound ester, 0.67 mmol/g, was prepared from −200+400 mesh copolymer containing 2.00 mmol/g of chloromethyl groups. [c] Polymer-bound ester, 1.08 mmol/g, was prepared from −60+100 mesh copolymer containing 1.10 mmol/g of chloromethyl groups.

Table II. Effect of Degree of Esterification on Yields from Enolate Acylation with p-Nitrobenzoyl Chloride[a]

esterification time, days	mmol of ester/g	% yield[b] 6a	8	9
1	0.46	99	0	0
2	0.76	66	10	24
3	0.89	45	17	35
4	0.98	43	17	38

[a] Starting polymer was macroporous, −60+100 mesh, and contained 20 wt % divinylbenzene and 1.10 mmol/g of chloromethyl groups. [b] Determined by GC.

Table III. Recycling of 10% Cross-linked Gel Polymer for Ester Enolate Acylation with p-Nitrobenzoyl Chloride

cycle	mmol of ester/g	% yield of 6a[a]
1	0.67	87
2	0.42	88
3	0.39	90

[a] Determined by GC and based on polymer-bound ester.

One batch of the recovered 10% cross-linked gel polymer from a p-nitrobenzoyl chloride acylation was recycled twice as follows. Recovered polymer was washed thoroughly and dried. The hydroxymethyl groups were reesterified by successive treatments with 1.5 molar equiv of (triphenylmethyl)lithium in THF at −40 °C and 4 molar equiv of 3-phenylpropanoyl chloride followed by warming to 25 °C for 24 h. Enolate generation and acylation were carried out by the usual method. Results are given in Table III.

Room temperature enolate generation and trapping give much more self-condensation when attempted without a polymer support or with polystyrenes cross-linked with only 2-6% divinylbenzene. Treatment of 0.11 M benzyl 3-phenylpropanoate in THF[18] under the same conditions used with polymer-bound ester gave 19% of acylated product **6a** and 58% of self-condensation product 8. A 6% cross-linked copolymer containing 0.68 mmol/g of polymer-bound ester 1 (from 1.00 mmol/g of chloromethyl groups) gave 52% of p-nitrobenzoyl derivative **6a**, 17% of self-condensation product 8, and 27% of unreacted ester **9** under the standard conditions.

Use of more highly cross-linked polystyrene and low conversion esterifications brings polymer-bound ester enolates into the realm of practical organic synthesis. Yields of acylation and alkylation products are nearly quantitative based on starting polymer-bound ester, and the effective concentrations of ester in the reaction mixtures are ~0.1 M, enabling 0.1 mol scale laboratory synthesis.[19] Performance of enolate chemistry with unhindered esters at room temperature instead of −78 °C avoids one major drawback to its large-scale application. Another major drawback, the use of expensive organolithium bases, still needs to be overcome.

Registry No. 6a, 54914-77-1; **6b**, 2550-26-7; **7a**, 78308-00-6; **7b**, 56964-65-9; **8**, 5396-91-8; **9**, 103-25-3.

(18) The same effective concentration as in the polymer-supported reactions.

(19) Procedure: The polymer-bound 3-phenylpropanoic ester (175 g, 0.59 mmol/g, 100 mmol, 10% cross-linked polystyrene gel, −100+325 mesh) was stirred mechanically for 1 h in 500 mL of THF under nitrogen in a 2000-mL three-neck flask. A solution of 103 mmol of (triphenylmethyl)lithium,[17] prepared from equimolar amounts of triphenylmethane and n-butyllithium, in 500 mL of THF was added to the polymer mixture by syringe in a period of 3 min. After about 7 min the red color of the mixture had faded, and a solution of 220 mmol of p-nitrobenzoyl chloride in 50 mL of THF was added by syringe. The mixture was stirred for 12 h at room temperature. The polymer was separated by filtration through a fritted glass funnel and washed with 500 mL of THF/diethyl ether (3/1 v/v), 500 mL of THF/ethanol (3/1 v/v), and 500 mL of THF. Solvents were evaporated, and the residue was dried at 30 °C under vacuum. A mixture of the dried polymer, 500 mL of THF, 12 mL of 50% aqueous KOH, and 0.8 mL of tetra-n-butylammonium hydroxide (40% aqueous) was heated at reflux for 24 h. After cooling the polymer was filtered and washed with 500 mL of THF and 500 mL of ethanol. The combined filtrate was neutralized with 5 N HCl, acidified with 5 mL of concentrated HCl, and heated at reflux for 2 h. Solvents were evaporated, and the residue was chromatographed quickly over silica gel with CCl_4/C_6H_6 (9/1 v/v). The recovered 1-(4-nitrophenyl)-3-phenyl-1-propanone was crystallized from ethanol to give 20.1 g (79 mmol, 77%) of colorless plates, mp 73-75 °C uncorrected (lit.[20] mp 75-75 °C) whose ^1H NMR and IR spectra were identical with those of independently synthesized material.

(20) Fonken, G. S.; Johnson, W. S. *J. Am. Chem. Soc.* **1952**, *74*, 831.

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Friedel-Crafts Reactions of Ethyl Cyclopropanecarboxylate[1]

Summary: The reaction of ethyl cyclopropanecarboxylate with benzene in the presence of aluminum chloride gives 2-methyl-1-indanone in excellent yield.

Sir: The Friedel-Crafts reaction is one of the most useful methods for the formation of carbon bonds to aromatic

(1) Taken in part from the MS thesis of Linwood W. Zoller, III, University of Georgia, 1980. Presented at the combined Southeast-Southwest Regional Meeting of the American Chemical Society, New Orleans, Dec 10-13, 1980; American Chemical Society: Washington, DC; Abstr. 478.

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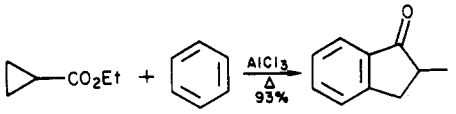
rings.[2] The electrophiles commonly used in this reaction are derived from alkyl halides, alcohols, alkenes, acid chlorides and anhydrides, carboxylic acids, and nitriles.[2] Esters are not widely utilized because of competitive acylation and alkylation[3] although lactones are useful precursors of cyclic ketones. For example, 1-tetralone and 1-indanone are efficiently prepared from butyrolactone[4] and propiolactone,[5] respectively. There are no reports on the use of cyclopropyl esters in the Friedel–Crafts reaction.

Ethyl cyclopropanecarboxylate reacts with an excess of aluminum chloride in refluxing benzene to give a 93% isolated yield of 2-methyl-1-indanone (eq 1). This is a



(1)

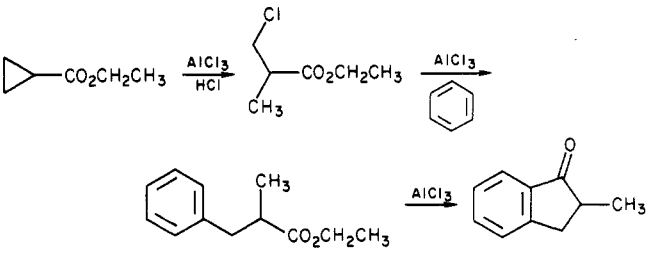
surprising result in view of the mixture of 2-methyl-1-indanone and 3-methyl-1-indanone obtained from the reaction of cyclopropanecarboxylic acid chloride with benzene under $AlCl_3$ catalaysis.[6] This latter reaction proceeds via cyclopropyl phenyl ketone[6] so that clearly the reaction of eq 1 does not involve this intermediate.

In an attempt to isolate intermediates in this novel reaction, the cyclopropyl ester and $AlCl_3$ were allowed to react in benzene at room temperature. Several products were isolated by preparative gas chromatography (SE-30 column) and identified by proton NMR and mass spectrometric analysis as ethyl α-methyl-β-phenylpropionate, ethyl β-chloro-α-methylpropionate, diethylbenzene, and triethylbenzene. In addition, 2-methyl-1-indanone was present in a small amount.

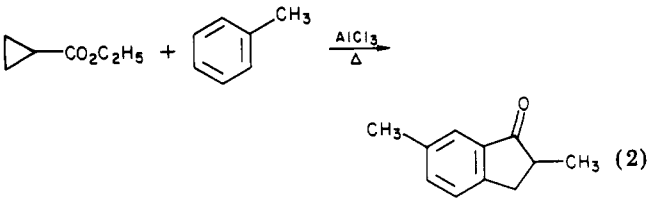
Examination of the effect of changing the ratio of aluminum chloride to ethyl cyclopropanecarboxylate gives further evidence of reaction intermediates. A reaction employing 3.6 molar equiv of $AlCl_3$ relative to the cyclopropyl ester gives 2-methyl-1-indanone in 93% yield. This same product is obtained in only 28% yield (average of two runs) from another reaction identical in all respects except that 2.0 molar equiv of $AlCl_3$ was used. 2-Methyl-3-phenylpropionic acid[7] also was obtained in 21% yield (average of two runs). Furthermore, the use of 1.0 molar equiv of $AlCl_3$ leads to no substituted benzene products.

The opening of ethyl cyclopropanecarboxylate apparently requires both aluminum chloride and hydrogen chloride. Exposure of the cyclopropyl ester to $AlCl_3$ in CH_2Cl_2 for 24 h at room temperature or reflux followed by workup gives a quantitative recovery of starting material[8] even though TLC analysis of the reaction mixture showed no starting material. This implies the formation of a stable complex between the cyclopropyl ester and $AlCl_3$.[9] Anhydrous HCl was bubbled into another reaction of the ester and $AlCl_3$ in CH_2Cl_2 at room temperature, and this reaction mixture was allowed to stir for 4 days. An 85% yield of a 44:56 mixture of ethyl β-chloro-α-methylpropionate[7] and the corresponding acid[7] were obtained. The $AlCl_3$ complex must have reacted with HCl to give the chloro compounds.

Scheme I. Proposed Reaction Mechanism



These results allow the formulation of a plausible reaction mechanism as that shown in Scheme I. Ring opening of the cyclopropane yields the chloro ester which then alkylates benzene. Intramolecular acylation gives the indanone product. Additional support for a mechanism involving alkylation followed by acylation is obtained from the reaction of toluene with ethyl cyclopropanecarboxylate. Several products are obtained but the major component is 2,6-dimethyl-1-indanone[7] isolated in 67% yield (eq 2).



(2)

Because of the directive effects of a methyl group in electrophilic aromatic substitution reactions,[2] initial bonding to toluene should occur para to the methyl group. The major product clearly results from initial alkylation and not acylation.

Other aromatic substrates also react with ethyl cyclopropanecarboxylate in the presence of $AlCl_3$ to give the substituted 1-indanones. For example, chlorobenzene, cumene, ethylbenzene, and fluorobenzene each react with the cyclopropyl ester and aluminum chloride to give substituted 2-methyl-1-indanones. These products are being fully characterized and full details will be included in the full paper.

Solvents can be used for the reaction of ethyl cyclopropanecarboxylate with benzene although the yield of indanone product is lower than that obtained with benzene as a solvent. For example, hexane allows the isolation of a 56% yield of product, while the yield is 68% when *o*-dichlorobenzene is used as the solvent. Separation problems cause a depressed yield particularly in the latter case. Large substrates should give better results.

The scope of the reaction is currently under investigation as well as a detailed study of the use of the α-indanone products as synthetic intermediates.

Preparation of 2-Methyl-1-indanone. Anhydrous $AlCl_3$ (48 g, 360 mmol) was added in portions over a 20-min period to a solution of ethyl cyclopropanecarboxylate (11.4 g, 100 mmol) in 80 mL of dry benzene. The reaction mixture was allowed to reflux for 16 h, cooled, and poured into 50 mL of concentrated HCl and 100 g of ice. The aqueous layer was saturated with NaCl, the organic layer was separated, and the aqueous phase was extracted with two 50-mL portions of ether. The combined organic layers were washed sequentially with two 50-mL portions of brine and 25 mL of saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated to give after distillation 13.6 g (93%) of the pure product:[10] 108–110 °C (5 mm);

(2) Olah, G. A. "Friedel–Crafts Chemistry"; Wiley: New York, 1973.
(3) Reference 2, p 49.
(4) (a) Truce, W. E.; Olson, C. E. *J. Am. Chem. Soc.* **1952**, *74*, 4721. (b) Olson, C. E.; Bader, A. R. "Organic Syntheses", Collect. Vol. 4; Wiley: New York, 1963; p 898.
(5) Rinehart, K. L., Jr.; Gustafson, D. H. *J. Org. Chem.* **1960**, *25*, 1836.
(6) Combaut, G.; Giral, L. *Bull. Soc. Chim. Fr.* **1970**, 3710.
(7) This compound was identified by ^1H NMR, ^{13}C NMR, MS, and IR spectral determinations.
(8) Some cyclopropanecarboxylic acid was obtained in addition to the ester from the reaction mixture which was heated.
(9) Complexes of this type have been proposed in the reaction of cyclopropyl ketones with $AlCl_3$.[6]
(10) The ^1H NMR and IR spectra are identical with the published values.[6]

^{1}H NMR (CCl_4) δ 1.3 (3 H, d, J = 7 Hz), 2.4–2.9 (2 H, m), 3.4 (1 H, dd, J = 8 Hz, J' = 18 Hz), 7.0–7.7 (4 H, m); IR (NaCl) 1710 cm^{-1} (C=O); mass spectrum (relative abundance), m/e 146 (P, 70), 131 (100), 115 (45), 103 (41), 91 (32), 77 (30), 65 (32), 51 (35), 39 (39).

Registry No. 2-Methyl-3-phenylpropionic acid, 1009-67-2; β-chloro-α-methylpropionic acid, 16674-04-7; ethyl β-chloro-α-methylpropionate, 922-29-2; 2,6-dimethyl-1-indanone, 66309-83-9; toluene, 108-88-3; 2-methyl-1-indanone, 17496-14-9; ethyl cyclpropanecarboxylate, 4606-07-9; benzene, 71-43-2.

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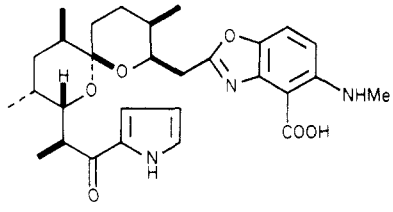
Preparation and Lithiation of *N*-(*N*,*N*-Dimethylamino)pyrrole: A Useful Reagent for the Preparation of 2-Acylpyrroles

Summary: *N*-(*N*,*N*-Dimethylamino)pyrrole can be efficiently lithiated at C(2) with butyllithium and transformed into the corresponding Grignard reagent, which upon condensation with pyridinethiol esters and reductive cleavage of the nitrogen–nitrogen bond provides direct access to 2-acylpyrroles.

Sir: In connection with our synthetic efforts in the antibiotic area [cf. A-23187 (1)],[1] we required a mild method for the preparation of 2-acylpyrroles from a suitable pyrrole derivative. Essential to our scheme was the proper choice



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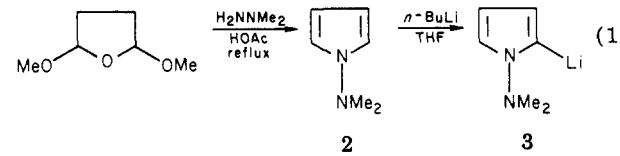
of a protecting group for the pyrrole N–H bond which would facilitate and stabilize carbanion formation at C(2) and, more importantly, be easily removed under extremely mild conditions. The lack of suitably protected pyrrole derivatives[2] which would be amenable to our needs led us to examine the feasibility of employing the previously unreported pyrrole, *N*-(*N*,*N*-dimethylamino)pyrrole (**2**). We report the preparation and facile lithiation of **2** (eq 1) and the utilization of **3** in the preparation of 2-acylpyrroles.

N-(*N*,*N*-Dimethylamino)pyrrole (**2**), bp 138–140 °C (distilled from calcium hydride) [^{1}H NMR (CCl_4) δ 2.76 (s, 3 H), 5.81 (t, 1 H), 6.60 (t, 1 H)] was prepared in 57% yield by refluxing (3 h) 2,5-dimethoxytetrahydrofuran and



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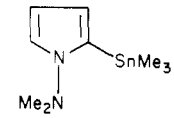
unsym-dimethylhydrazine in acetic acid. Lithiation of **2** (1 M in dry tetrahydrofuran) proceeded smoothly (2 h) with 1.0 equiv of *n*-butyllithium, generating the 2-lithiopyrrole **3**. Trapping of **3** with trimethyltin chloride gave 2-(trimethylstannyl)pyrrole **4**, bp 68–70 °C (2.0 mmHg),



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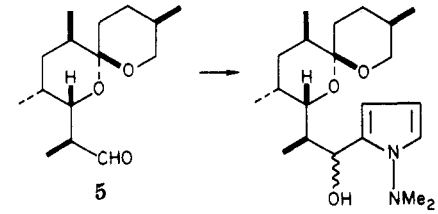
in approximately 80% yield. Regeneration of **3** from **4** could be efficiently carried out by treating a THF solution of **4** cooled to −78 °C with 1.0 equiv of *n*-butyllithium. Trapping of **3** with heptanal and aldehyde **5**[1b] gave rise to adducts **6** (75%) and **7** (70%), respectively. Oxidation (MnO_2, CH_3CN) of **6** afforded (70%) the corresponding ketone which when subjected to cleavage of the nitrogen–nitrogen bond [$Cr_2(OAc)_4 \cdot 2H_2O$[3] (3.0 equiv), EtOH, RT, 12 h] gave a 95% yield of the 2-acylpyrrole **8**. Attempts to reductively cleave the N–N bond under hydrogenolysis conditions (H_2, 10% Pd/C, EtOH) were not encouraging.



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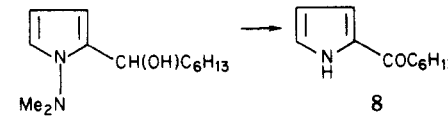

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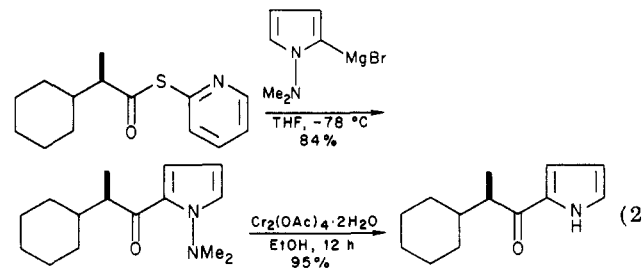
A direct route to 2-acylpyrroles was achieved by condensation of the Grignard reagent derived from **3** (prepared at 0 °C by treatment of **3** with 1.0 equiv of anhydrous $MgBr_2$ in tetrahydrofuran) with pyridinethiol esters[4] followed by clipping of the N–N bond with chromous acetate (cf. eq 2). Yields for the latter step are generally



(2)

in excess of 95%. Application of this two-step sequence to substrates **9**[5] and **10** provided **11** and **12**, respectively, in excellent overall yield.[6]

(1) (a) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537. (b) Grieco, P. A.; Williams, E.; Kanai, K. In "Organic Synthesis Today and Tomorrow (IUPAC)"; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon Press: New York, 1981; pp 187–196. (c) Also see Evans, D. A.; Sacks, C. E.; Kleschich, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6798.
(2) For α lithiation of N-substituted pyrroles, see Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 21. Also see Hasan, I.; Marinelli, E. R.; Lin, C. L.-C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.
(3) Jolly, W. L. "The Synthesis and Characterization of Inorganic Compounds"; Prentice-Hall: Englewood, NJ, 1970; p 442.
(4) Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763 and references cited therein.
(5) The transformation of **9** into **11** was carried out at −10 °C.

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