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Synthesis, Reactions, and Properties of 1-Phenyl-2-Propen-1-ol Derivatives

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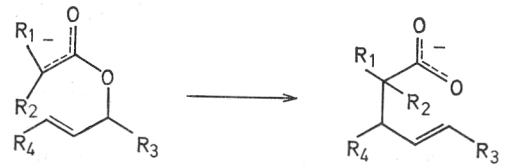
The synthesis and chemical properties of some 1-phenyl-2--propen-1-ol derivatives are described, with emphasis on the synthesis of 1-phenyl-2-propenyl type alkylating agents. Alkylation reactions of the ester enolate derived from methyl isobutyrate with isomeric 1-chloro-1-phenyl-2-propene and 1-chloro-3-phenyl-2--propene, to give the same final product, is discussed in some detail.

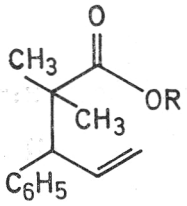
INTRODUCTION

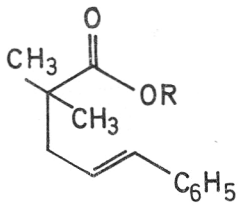
The regiospecific thermal rearrangement of enolate carbanions derived from allylic esters (eq 1), first described some years ago[1–3], has proved to be of general synthetic usefulness.



(1)

During the course of a recent study related to this symmetry-allowed [3,3] sigmatropic rearrangement, we required an independent method for the preparation of isomeric compounds **1** and **2**, otherwise obtained by a thermal rearrangement of allylic esters of isobutyric acid.





1 , R = H

3 , R = CH_3

2 , R = H

4 , R = CH_3

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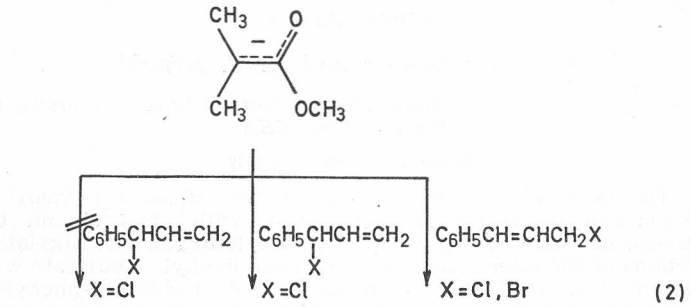
Following the well described procedures for the intermolecular alkylations of some other ester enolates with alkyl halides[4-6], we have been able to prepare the ester derivative **4** of the acid **2** (eq 2). Alkylation of the ester enolate derived from methyl isobutyrate (by the action of lithium diisopropylamide as a base) with 1-halo-3-phenyl-2-propene (cinnamyl halides), in THF solutions, proceeds readily at 20 °C to give **4**. However, under analogous conditions, alkylation with 1-chloro-1-phenyl-2-propene gave the same isomer **4**, instead of **3**. It is, therefore, obvious that ester derivatives of **1** cannot be prepared by direct, intermolecular alkylation reactions.



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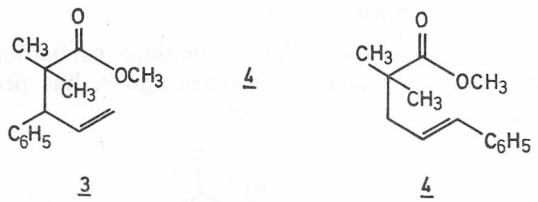
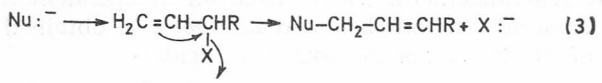


3 4

From a mechanistic point of view, there are two possible explanations for the preferential formation of **4** in alkylations described by eq 2:

(*a*) the reaction proceeds through the S_N2' mechanism (eq 3)[7-9], or

(*b*) a carbonium type of reaction is involved (eq 4)[10]



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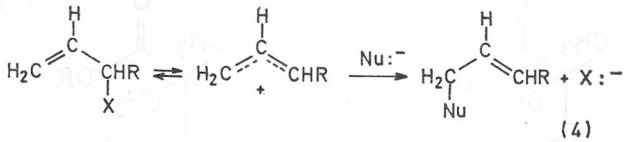


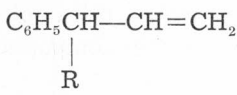
(4)

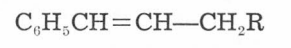
Nu:⁻ = $(CH_3)_2C{=}\overset{-}{C}{-}\overset{O}{\overset{\|}{C}}{-}OCH_3$, R = C_6H_5, X = Cl

The variety of pathways possible for the reactions of allylic halides makes an unambigous determination of the mechanism extremely difficult. Either of these mechanisms could have taken place in the alkylation of an ester enolate with a secondary allylic halide bearing a phenyl group.

In our search for an efficient and easily prepared alkylating agent of

the 1-phenyl-2-propenyl type, to be used in reactions described by eq 2, we have examined in some detail the preparation of several 1-phenyl-2-propen-1-ol (**5**) derivatives. While the acetate **6**, isobutyrate **7**, and the trifluoroacetate **8** could be prepared under carefully controlled conditions, we were unable to prepare the tosylate **9**, mesylate **10**, or the 1-chloro-1-phenyl-2-propene **11** in pure form. The reaction of **5** with acetic anhydride, at 80 °C, exclusively





5, R = OH
6, R = $OCOCH_3$
7, R = $OCOCH(CH_3)_2$
8, R = $OCOCF_3$
9, R = $OSO_2C_6H_4CH_3$
10, R = OSO_2CH_3
11, R = Cl

12, R = $OCOCH(CH_3)_2$
13, R = $OCOCF_3$
14, R = $OSO_2C_6H_4CH_3$
15, R = OSO_2CH_3
16, R = Cl

produced **6**. Pure isobutyrate **7** could not be made by any of the classical methods for the preparation of esters. Its isomer **12** always formed in substantial quantities. We found that pure **7** can be made in a reaction of **5** with *n*-BuLi, followed by the addition of isobutyryl chloride at —78 °C. Once formed it is a stable substance at room temperature.

Our search for a compound bearing a good leaving group, which can be used in alkylation reactions described previously (eq 2), led us to focus our attention on trifluoroacetates, tosylates, mesylates, and chlorides.

While at higher temperatures mixtures of isomeric trifluoroacetates **8** and **13** were obtained, only **8** forms in a reaction of **5** with trifluoroacetic anhydride at —78 °C. Unfortunately, trifluoroacetates could not be used as alkylating agents because nucleophiles (e. g., CH_3O^-) attack it, preferentially at the carbon atom of the carbonyl group. Furthermore, they decompose on standing.

All attempts to synthesize the tosylate **9**, and the mesylate **10** in pure form, were unsuccessful. Reaction of **5** with methanesulfonyl chloride gave only **15**, while treatement of **5** with *n*-BuLi followed by methanesulfonyl chloride (or methanesulfonyl chloride and lithium chloride in hexamethylphosphoramide)[11] gave mixtures of **10** and **15**, with **15** predominating in large excess. Mesylate **15** can be kept for a limited period of time in ether, and at low temperature (—20 °C). It decomposes rapidly at room temperature. Under the same experimental conditions we could observe no reaction of **5** with *p*-toluenesulfonyl chloride to produce **9**, **14** or mixtures of both.

In the case of chlorides our results are at variance with those reported previously[12]. A reaction of **5** with thionyl chloride in triethylamine gave two products, **11** and **16**. Even after two fractional distillations, a mixture of isomeric allylic chlorides was obtained, with **11** predominating in sufficiently large excess to be successfuly used in alkylation reactions.

The profound difference in the NMR spectra of the isomeric substances described above, enabled us to differentiate them easily, as well as to determine exact ratios when mixtures were obtained.

It has been previously proposed[12] that in the reaction of the alcohol **5** with thionyl chloride an intermediate chlorosulphinate forms first. A bimolecular (S_N2) attack of the chloride ion gives **11** then, which rearranges intramolecularly to produce the cinnamyl isomer **16.** In the formation of mesylates, isobutyrates, and trifluoroacetates an ester bond forms with no breakage of the carbon-oxygen linkage of the alcoholic part. It is, therefore, conceivable that 1-phenyl-2-propenyl products form first, followed by an intramolecular rearrangement of the intermediate to give cinnamyl type compounds as final products.

EXPERIMENTAL

All solvents were purified by standard methods and stored over appropriate drying agents. Cinnamyl alcohol (Aldrich), cinnamyl bromide (Aldrich), and *n*-BuLi (1.6 molar solution in hexane) (Aldrich) were used without further purification. Methyl isobutyrate was prepared by a standard procedure using methanol, isobutyric acid and catalytic amounts of sulfuric acid. Lithium diisopropylamide was formed in situ from *n*-BuLi and diisopropylamine.[13] 1-Phenyl-2-propen-1-ol formed on addition of the Grignard reagent derived from bromobenzene, to acrolein.[14] Isobutyryl chloride was prepared from isobutyric acid and thionyl chloride.

The ^{1}H NMR spectra were recorded on a Varian A-56/60 spectrometer, and all chemical shifts are given in ppm downfield from tetramethylsilane (δ scale). The IR spectra were recorded as liquid films on sodium chloride plates with a Beckman IR-5A spectrophotometer.

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, USA.

1-Chloro-3-phenyl-2-propene (**16**) *and 1-Chloro-1-phenyl-2-propene* (**11**)

Compound **16** was prepared according to Valkanas et al.[12] from cinnamyl alcohol and thionyl chloride in 55.6% yield, b. p. 78 °C—80 °C (0.75 mm Hg*).

Compound **11** was prepared according to the same general procedure from 1-phenyl-2-propen-1-ol and thionyl chloride in 35.8% yield, b. p. 72 °C (2 mm Hg). This product contained 20% of **16**.

Methyl 2,2-Dimethyl-5-phenyl-4-pentenoate (**4**)

Methyl isobutyrate (2.04 g, 20 mmol) was added, dropwise and with stirring, to a solution of lithium diisopropylamide (24 mmol) in THF (5.5 ml) at —78 °C and under argon. The reaction mixture was stirred for 30 minutes, and a solution of cinnamyl chloride (3.66 g, 24 mmol) in THF (10 ml) was added dropwise at —78 °C. The mixture was allowed to warm to room temperature and was then stirred for 2 hours during which a precipitate formed. Cold HCl (40 ml, 1M) was then added, the layers separated, and the water layer extracted with ether (3 × 30 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (40 ml), water (40 ml), and dried ($MgSO_4$). Evaporation of the solvent on a rotary evaporator gave yellow oil (3.42 g). The crude product was purified on a column of alumina (hexane as a solvent) to give the pure ester **4**; 2.81 g (64.4%), b. p. 99 °C—100 °C (1 mm Hg).

^{1}H NMR ($CDCl_3$) δ 1.17 (s, 6 H), 2.36 (d, 2 H), 3.54 (s, 3 H), 6.17 (m, 2 H), 7.22 (m, 5 H).

Anal. $C_{14}H_{18}O_2$ (218.298) calc'd.: C 77.03; H 8.31%
found: C 77.33; H 8.40%

The same procedure, using cinnamyl bromide (4.73 g, 24 mmol) as the alkylating agent, gave 3.52 g (80.6%) of the desired ester **4**.

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* 1 mm Hg ≈ 133.322 Pa

Alkylation of the Carbanion Derived from Methyl Isobutyrate with the Mixture of 1-Chloro-1-phenyl-2-propene (**11**) *and 1-Chloro-3-phenyl-2-propene* (**16**) (8 : 2)

Methyl isobutyrate (2.04 g, 20 mmol) was converted into its anion with lithium diisopropylamide (24 mmol) as described for the preparation of **4**. It was alkylated with a mixture of **11** and **16** (8 : 2) to give 3.5 g of yellow oil whose ^{1}H NMR spectrum was identical to that of methyl 2,2-dimethyl-4-pentenoate (**4**).

1-Phenyl-2-propenyl Isobutyrate (**7**)

1-Phenyl-2-propen-1-ol (**5**) (5.37 g, 40 mmol) was added, dropwise and with stirring, to a 1.6 molar solution of *n*-BuLi in hexane (27.5 ml, 44 mmol) and THF (16.5 ml) at —78 °C and under argon. The dark yellow reaction mixture was stirred for 30 minutes, and isobutyryl chloride (4.69 g, 44 mmol) was added dropwise at —78 °C. The light-yellow mixture was allowed to warm to room temperature and was then stirred for 2 hours during which a white precipitate formed. It was then poured onto ice, the layers separated, and the aqueous layer extracted with ether (2 × 30 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (50 ml), water (50 ml) and dried (Mg SO_4). Evaporation of the solvents on a rotary evaporator gave a colorless liquid (8.05 g, 98.5%) whose NMR spectrum was indistinguishable from the pure product. Distillation gave the pure ester **7**; 7.40 g (90.6%); b. p. 54 °C (0.05 mm Hg).

^{1}H NMR ($CDCl_3$) δ 1.08 (d) and 1.11 (d) (6 H), 2.51 (septet, 1 H), 5.09 (m, 1 H), 5.36 (m, 1 H), 5.89 (m, 1 H), 6.28 (m, 1 H), 7.24 (m, 5 H).

Anal. $C_{13}H_{16}O_2$ (204.271) calc'd.: C 76.44; H 7.90%
found: C 76.13; H 7.82%

3-Phenyl-2-propenyl Trifluoroacetate (**13**)

A solution of trifluoroacetic anhydride (8.40 g, 40 mmol) in dry ether (15 ml) was added dropwise over a period of 15 minutes, to a stirred solution of cinnamyl alcohol (4.97 g, 37 mmol), anhydrous triethylamine (4.05 g, 40 mmol) and dry ether (30 ml) at —10 °C. The mixture was stirred for an additional 15 minutes, poured onto ice (50 g) and the layers separated. The ethereal layer was washed with cold water (2 × 30 ml), saturated sodium bicarbonate solution (50 ml), cold water (50 ml), and dried ($MgSO_4$). Evaporation of the solvent on a rotary evaporator gave the liquid product. Distillation gave the expected colorless ester which decomposes on standing; 7.25 g (85%); b. p. 76 °C—77 °C (0.6 mm Hg).

IR (neat film) ν_{max} 1786 (C=O); 1658 (C=C, weak); 1493, 1449, 1389 (C=C, aromatic); 1351 (C—O); 1220, 1149 (CF_3); 965 (*trans* CH=CH); 736, 729, 689 (CH, aromatic) cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 4.80 (d, 2 H), 6.32 (m, 2 H), 7.25 (s, broad, 5 H).

Anal. $C_{11}H_9F_3O_2$ (230.187) calc'd.: C 57.40; H 3.94; F 24.76%
found: C 57.55; H 4.02; F 24.73%

1-Phenyl-2-propenyl Trifluoroacetate (**8**)

In a manner similar to that described for **13**, trifluoroacetic anhydride (11.55 g, 55 mmol) in dry ether (15 ml) was added to a solution of 1-phenyl-2-propen-1-ol (**5**) (4.97 g, 37 mmol), anhydrous triethylamine (5.57 g, 55 mmol) and dry ether (50 ml) at —78 °C. Fractional distillation of the crude product gave the expected ester **8** which decomposes on standing; 4.60 g (54%); b. p. 46 °C—47 °C (0.75 mm Hg).

IR (neat film) ν_{max} 1786 (C=O); 1493, 1449, 1389 (C=C, aromatic); 1370 (C—O); 1220, 1149 (CF_3); 893 (broad, trans CH=CH and CH_2=CH out of plane bending); 758, 727, 695 (CH, aromatic) cm^{-1}.

^{1}H NMR ($CDCl_3$) δ 5.20 (m, 1 H), 5.43 (m, 1 H), 5.92 (m, 1 H), 6.33 (m, 1 H), 7.29 (s, broad, 5 H).

Anal. $C_{11}H_9F_3O_2$ (230.187) calc'd.: C 57.40; H 3.94; F 24.76%
found: C 57.61; H 4.04; F 25.08%

Further distillation gave 3-phenyl-2-propenyl trifluoroacetate; 2.10 g; b. p. 76 °C—77 °C (0.6 mm Hg).

3-Phenyl-2-propenyl Mesylate (**15**)

Freshly distilled methanesulfonyl chloride (5.10 g, 44.5 mmol) was added, dropwise, to a solution of cinnamyl alcohol (5.00 g, 37.3 mmol) in dry pyridine (45 ml) at 0 °C. The solution was stirred for 15 minutes at 0 °C, and left for an additional 24 hours at —20 °C. It was poured onto ice (120 g) containing concentrated HCl (45 ml). The aqueous mixture was extracted with ether (4 × 30 ml), and the combined ethereal layers washed with saturated sodium bicarbonate solution (50 ml), water (50 ml), and dried ($MgSO_4$). Evaporation of the solvent on a rotary evaporator at 20 °C gave yellow oil; 2.60 g (33%).

IR (neat film) ν_{max} 1600 (C=C, weak); 1580, 1445 (C=C, aromatic); 1370, 1176 (SO_2); 965 (trans CH=CH); 743, 698 (CH, aromatic) cm^{-1}.

^1H NMR δ 3.28 (s, 3 H), 4.05 (d, 2 H), 6.25 (m, 2 H), 7.20 (s, broad, 5 H).

The same general procedure using 1-phenyl-2-propen-1-ol (**5**), instead of cinnamyl alcohol, gave a mixture of **15** and **10** (6 : 4).

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SAŽETAK

Sinteze, reakcije i svojstva derivata 1-fenil-2-propen-1-ola

S. T. Kulenović i R. T. Arnold

Opisane su sinteze i kemijska svojstva nekih derivata 1-fenil-2-propen-1-ola. Posebna je pažnja posvećena pripravi reagensa za alkiliranje 1-fenil-2-propenilnog tipa. Opisane su i reakcije alkilacije enolata metilnog estera izomaslačne kiseline s 1-kloro-1-fenil-2-propenom i 1-kloro-3-fenil-2-propenom pri čemu je dobiven identičan konačni produkt.

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