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(13) Other acids have not been examined.
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(21) Prepared from acetophenone by the method of ref 19.
(22) Prepared by the general method of ref 19. Cf. *Chem. Abstr.*, **75**, 129556p (1971).
(23) This acetal [bp 74–76 °C (4 mm)] was prepared by the general method of ref 19. Anal. Calcd for $C_{11}H_{24}O_2$: C, 70.16; H, 12.85. Found: C, 70.33; H, 12.81.

Regiospecific Synthesis of 2,3-Disubstituted Furans, Pyrroles, and Thiophenes. Claisen Ortho Ester Rearrangement of Heterocyclic Glycolates[1]

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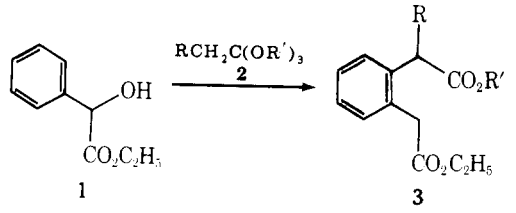
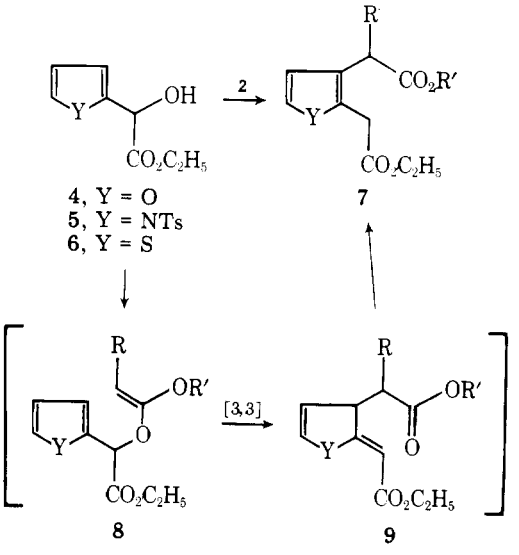
The [3,3] sigmatropic rearrangement of allyl vinyl ethers provides a versatile method for the construction of new carbon to carbon bonds with high regio- and stereospecificity.[2] Although [3,3] sigmatropic rearrangements of systems in which the *vinyl* moiety is formally incorporated in an aromatic ring (allyl *phenyl* ethers) are well known,[3] [3,3] sigmatropic rearrangements of systems in which the *allyl* moiety is formally incorporated in an aromatic ring (*benzyl* vinyl ethers) are not generally possible.[4]

We recently demonstrated that the Claisen ortho ester rearrangement of benzyl alcohols is facilitated by a carbethoxy group at the benzylic position; namely, ethyl mandelate (**1**) readily undergoes a Claisen ortho ester rearrangement with ortho esters **2** to give ortho-disubstituted arenes **3**, whereas benzyl alcohol fails to rearrange under the same conditions.[5]



1 **3**

We now wish to report that the Claisen ortho ester rearrangement of ethyl 2-furanglycolate (**4**), ethyl *N*-tosyl-2-pyrroleglycolate (**5**), or ethyl 2-thiopheneglycolate (**6**) with ortho esters **2** provides an extremely convenient method for the regiospecific synthesis of 2,3-disubstituted furans,[6] pyrroles, or thiophenes. The results of these studies are summarized in Table I.[7]



The above transformation is amenable to the synthesis of 2,3-disubstituted heterocycles for a number of reasons: (1) a variety of heterocyclic glycolates and ortho esters[8] are readily available; (2) the reaction conditions are compatible with a wide array of functionality; (3) the reaction provides a method for the regiospecific synthesis of substituted heterocycles that would be difficultly accessible by alternative methods; (4) the carbethoxy groups provide convenient handles for subsequent synthetic transformations; and (5) no ester exchange occurs under the reaction conditions (entry g of Table I); hence, differentiation of the two ester groups is possible.[9]

The influence of the carbethoxy group in facilitating the reaction is presumably due to the increased stabilization of the putative intermediate **9** formed by [3,3] sigmatropic rearrangement of the benzyl vinyl ether **8**.[5]

Attempts to effect Claisen ortho ester rearrangement of **4** or **6** with trimethyl orthoisobutyrate led to complex mixtures accompanied by extensive decomposition. This outcome is possibly caused by homolytic scission of the benzylic carbon–oxygen bond[4a-e] due to the increased stability of the resulting methyl-α-isobutyryl radical.[10]

The preparation of the 2-heterocyclic glycolates is quite straightforward. Ethyl 2-furanglycolate (**4**) was prepared from furfural cyanohydrin.[11] Ethyl *N*-tosyl-2-pyrroleglycolate (**5**)

0022-3263/79/1944-1885$01.00/0

Table I. Claisen Ortho Ester Rearrangement of Heterocyclic Glycolates

entry	glycolate Y	registry no.	ortho ester R	ortho ester R′	registry no.	reaction conditions[a]	% yield[b] of 7	registry no.
a	O	19377-72-1	H	Et	78-39-7	A	63	69551-43-5
b	O		Me	Et	115-80-0	A	75	69551-44-6
c	NTs	69551-42-4	H	Et		B	21	69551-45-7
d	NTs		Me	Et		B	18	69551-46-8
e	S	62323-55-1	H	Et		A	61	38447-34-6
f	S		Me	Et		A	50	69551-47-9
g	S		*n*-Pr	Me	13820-09-2	C	61	69551-48-0

[a] Reaction conditions: (A) 20 equiv of ortho ester and 0.1 equiv of hexanoic acid, 12 h reflux, 6 h at 185 °C, no added $C_6H_4Cl_2$; (B) 10 equiv of ortho ester and 0.1 equiv of hexanoic acid, 8 h reflux, $C_6H_4Cl_2$ added, 4 h at 210 °C; (C) 5 equiv of ortho ester and 0.1 equiv of hexanoic acid, 8 h at 170 °C, $C_6H_4Cl_2$ added, 10 h at 200 °C. [b] See ref 7.

was prepared from ethyl 2-pyrrolegloxylate (**10**)[12] by reaction with NaH–TsCl, followed by reduction with $NaBH_4$. As in the 3-indoleglycolate case,[5] tosylation of the nitrogen is necessary to prevent decomposition of the pyrrole. The reduction of ethyl *N*-tosyl-2-pyrroleglyoxylate (**11**) requires the use of a limited amount of $NaBH_4$ and short reaction times in order to prevent overreduction. Ethyl 2-thiopheneglycolate (**6**) was prepared from ethyl 2-thiopheneglyoxylate (**12**)[13] by reduction with $NaBH_4$; again, the reduction requires careful monitoring.

No attempts were made to investigate the Claisen ortho ester rearrangement of 3-furanglycolates, 3-pyrroleglycolates, or 3-thiopheneglycolates. It is anticipated that such systems would be converted to mixtures of 2,3- and 3,4-disubstituted heterocycles.[14]

Experimental Section

^{1}H NMR spectra were recorded on a Varian Associates EM 360 spectrometer using tetramethylsilane as an internal standard; coupling constants are reported in hertz. IR spectra were recorded on a Beckman Acculab 4. High-resolution mass spectra were obtained on a AEI MS9 spectrometer. Purifications were carried out by either gravity column chromatography utilizing silica gel 60 (200–500 μm) with hexane–ether eluent or flash chromatography[15] utilizing silica gel 60 (40–63 μm) with hexane–ethyl acetate eluent; the latter technique proved to be superior. Boiling points are given for compounds purified by evaporative distillation on a Kugelrohr apparatus and are uncorrected. Melting points are uncorrected. Spectral data and yields refer to isolated products which were purified by column chromatography and monitored by TLC, followed by complete removal of solvents in vacuo. All purified compounds were homogeneous on TLC (10% EtOAc–hexane). Yields were not optimized.

Ethyl 2-furanglycolate (4) was prepared by the method of Degering and Boatright:[11] bp 82 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, *J* = 7 Hz, 3 H), 3.55 (s, OH, 1 H), 4.25 (q, *J* = 7 Hz, 2 H), 5.20 (s, –C**H**(OH)CO_2Et, 1 H), 6.35 (m, 2 H), 7.40 (m, 1 H).

Ethyl *N*-Tosyl-2-pyrroleglyoxylate (11). To a suspension of NaH (0.50 g, 10.5 mmol) in dry THF (35 mL) under an atmosphere of argon was added a solution of ethyl 2-pyrrolegloxylate (**10**)[12] (1.17 g, 7.0 mmol) in THF (4 mL). A solution of *p*-toluenesulfonyl chloride (1.46 g, 7.7 mmol) in THF (4 mL) was added, and the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched with HOAc (0.5 mL), poured into saturated aqueous NH_4Cl, and extracted with ether (3 × 30 mL). The ether extracts were dried ($MgSO_4$), the ether was removed in vacuo, and the residue was purified by chromatography on silica gel (ether eluent), followed by crystallization from EtOH–H_2O: yield 1.19 g, 3.70 mmol (52%); mp 81–82 °C; ^{1}H NMR (CCl_4) δ 1.24 (t, *J* = 7 Hz, 3 H), 2.31 (s, 3 H), 4.20 (q, *J* = 7 Hz, 2 H), 6.25 (apparent t, *J* = 4 Hz, 1 H), 7.1–7.4 (m, 3 H), 7.6–8.0 (m, 3 H).

Ethyl *N*-Tosyl-2-pyrroleglycolate (5). The glyoxylate **11** (963 mg, 3.0 mmol) was dissolved in warm EtOH (40 mL), THF (20 mL) was added, and the solution was cooled to 0 °C; a solution of $NaBH_4$ (113 mg, 3.0 mmol) in H_2O (1 mL) was added, and the reaction mixture was stirred at 0 °C for 15 min and then quenched with HOAc (540 mg, 9.0 mmol). The solvents were removed in vacuo, and the residue was extracted with CH_2Cl_2 (2 × 25 mL). The extracts were dried ($MgSO_4$), the CH_2Cl_2 was removed in vacuo, and the residue was purified by chromatography on silica gel to give a colorless liquid: 915 mg, 2.83 mmol (95%); ^{1}H NMR (CCl_4) δ 1.19 (t, *J* = 7 Hz, 3 H), 2.29 (s, 3 H), 3.55 (br s, OH, 1 H), 4.15 (q, *J* = 7 Hz, 2 H), 5.58 (s, –C**H**(OH)CO_2Et, 1 H), 6.10 (m, 2 H), 7.05–7.31 (m, 3 H), 7.81 (d, *J* = 9 Hz, 2 H).

Ethyl 2-Thiopheneglycolate (6). To a solution of ethyl 2-thiopheneglyoxylate (**12**)[13] (460 mg, 2.50 mmol) in EtOH (10 mL) cooled to 0 °C was added a solution of $NaBH_4$ (47 mg, 1.2 mmol) in H_2O (0.5 mL). The reaction mixture was stirred for 5 min and treated with HOAc (300 mg, 5.0 mmol) and H_2O (5 mL). The majority of the solvents were removed in vacuo. The residue was extracted with CH_2Cl_2 (2 × 20 mL), the extracts were washed with brine and dried ($MgSO_4$), and the solvents were removed in vacuo to give a colorless liquid: 420 mg, 2.26 mmol (90%); ^{1}H NMR δ 1.30 (t, *J* = 7 Hz, 3 H), 3.60 (br s, OH, 1 H), 4.35 (q, *J* = 7 Hz, 2 H), 5.45 (s, –C**H**(OH)CO_2Et, 1 H), 6.95–7.40 (m, 3 H). Anal. $C_8H_{10}O_3S$: *m/e* calcd 186.0351, found 186.0356.

Diethyl 2,3-Furandiacetate (7a). A solution of ethyl 2-furanglycolate (**4**) (340 mg, 2.00 mmol), triethyl orthoacetate (6.5 g, 40 mmol), and hexanoic acid (23 mg, 0.2 mmol) in a 25-mL flask fitted with a 15-cm Vigreux column topped with a short-path distillation head was heated at reflux for 12 h with stirring in an argon atmosphere; ethanol was allowed to distill out of the reaction as it was formed. The Vigreux column was removed, the short-path distillation head was placed on the reaction flask, and heating was continued at 185 °C for 6 h. Excess ortho ester was removed in vacuo, and the residue was purified by column chromatography on silica gel (hexane–ether eluent) to give a colorless liquid: 302 mg, 1.26 mmol (63%); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7 Hz, 6 H), 3.45 (s, 2 H), 3.70 (s, 2 H), 4.20 (overlapping q, 4 H), 6.40 (d, *J* = 2 Hz, 1 H), 7.35 (d, *J* = 2 Hz, 1 H). Anal. $C_{12}H_{16}O_5$: *m/e* calcd 240.0998, found 240.1004.

Preparation of Furan 7b. Claisen ortho ester rearrangement of **4** (2.00 mmol) and triethyl orthopropionate (40.0 mmol) was carried out as described above; purification by column chromatography on silica gel (hexane–ether eluent) gave a colorless liquid: 381 mg, 1.49 mmol (75%); ^{1}H NMR ($CDCl_3$) δ 1.13 (t, *J* = 7 Hz), 1.17 (t, *J* = 7 Hz), and 1.30 (d, *J* = 6 Hz) (total 9 H), 3.45 (m) and 3.50 (s) (total 3 H), 4.00 (q, *J* = 7 Hz) and 4.05 (q, *J* = 7 Hz) (total 4 H), 6.30 (d, *J* = 2 Hz, 1 H), 7.23 (d, *J* = 2 Hz, 1 H).

Preparation of Thiophene 7e. Claisen ortho ester rearrangement of **6** (2.00 mmol) and triethyl orthoacetate (40.0 mmol) was carried out as described above; purification by column chromatography on silica gel (hexane–ether eluent) gave a colorless liquid: 313 mg, 1.22 mmol (61%); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7 Hz, 6 H), 3.60 (s, 2 H), 3.80 (s, 2 H), 4.13 (q, *J* = 7 Hz) and 4.15 (q, *J* = 7 Hz) (total 4 H), 6.92 (d, *J* = 5 Hz) and 7.15 (d, *J* = 5 Hz) (total 2 H). Anal. $C_{12}H_{16}O_4S$: *m/e* calcd 256.0769, found 256.0765.

Preparation of Thiophene 7f. Claisen ortho ester rearrangement of **6** (2.00 mmol) with triethyl orthopropionate (40.0 mmol) was carried out as described above; purification by column chromatography on silica gel (hexane–ether eluent) gave a colorless liquid: 270 mg, 1.00 mmol (50%); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, *J* = 7 Hz), 1.27 (t, *J* = 7 Hz), and 1.41 (d, *J* = 6 Hz) (total 9 H), 3.65 (m) and 3.76 (s) (total 3 H), 4.08 (q, *J* = 7 Hz) and 4.13 (q, *J* = 7 Hz) (total 4 H), 7.00 (d, *J* = 5 Hz) and 7.15 (d, *J* = 5 Hz) (total 2 H).

Diethyl *N*-Tosyl-2,3-pyrrolediacetate (7c). A solution of ethyl *N*-tosyl-2-pyrroleglycolate (**5**) (126 mg, 0.39 mmol), triethyl orthoacetate (650 mg, 4.0 mmol), and hexanoic acid (4 mg) was heated at reflux for 8 h under an argon atmosphere; *o*-dichlorobenzene (2 mL) was added, and heating at 210 °C was continued for 4 h. The excess ortho ester and *o*-dichlorobenzene was removed in vacuo (30 °C, 0.001

mm), and the residue was purified by column chromatography on silica gel (hexane–ether eluent) to give a colorless liquid: 32 mg, 0.082 mmol (21%); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 6 H), 2.40 (s, 3 H), 3.23 (s, 2 H), 3.76 (s, 2 H), 3.96 (q, J = 7 Hz) and 4.04 (q, J = 7 Hz) (total 4 H), 6.18 (m, 1 H), 7.08 (m) and 7.20 (d, J = 8 Hz) (total 3 H), 7.61 (d, J = 8 Hz, 2 H). Anal. $C_{19}H_{23}NO_4S$: m/e calcd 393.1244, found 393.1204.

Preparation of Pyrrole 7d. Claisen ortho ester rearrangement of **5** with triethyl orthopropionate was carried out as described above; purification by column chromatography on silica gel (hexane–ether eluent) gave a colorless liquid: 22 mg, 0.054 mmol (18%); ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz), 1.23 (t, J = 7 Hz), and 1.38 (d, J = 6 Hz) (total 9 H), 2.48 (s, 3 H), 3.45 (m, 1 H), 3.83 (s) and 4.05 (overlapping q) (total 6 H), 6.31 (m, 1 H), 7.15 (m) and 7.30 (d, J = 8 Hz) (total 3 H), 7.73 (d, J = 8 Hz, 2 H).

Preparation of Thiophene 7g. A solution of ethyl 2-thiopheneglycolate (372 mg, 2.00 mmol), trimethyl orthovalerate (1.62 g, 10.0 mmol), and hexanoic acid (23 mg, 0.20 mmol) in a 25-mL flask fitted with a 15-cm Vigreux column topped with a short-path distillation head was heated at 170 °C for 8 h with stirring in an argon atmosphere; methanol was allowed to distill out of the reaction as it was formed. The Vigreux column was removed, o-dichlorobenzene (2 mL) was added, the short-path distillation head was placed on the reaction flask, and heating was continued at 200 °C for 10 h. Excess ortho ester and o-dichlorobenzene were removed (25 °C, 0.001 mm), and the residue was purified by flash chromatography[15] on 40–63 μm silica gel (10% EtOAc–hexane eluent) to give a colorless liquid: 346 mg, 1.22 mmol (61%); no ester exchange could be detected by VPC (5% OV 101 or 5% DEGS) or ^{1}H NMR; ^{1}H NMR ($CDCl_3$) δ 0.80–1.50 (m) and 1.21 (t, J = 7 Hz) (total 10 H), 3.55 (s, 3 H), 3.62 (m) and 3.70 (s) (total 3 H), 4.11 (q, J = 7 Hz, 2 H), 6.92 (d, J = 5 Hz) and 7.09 (d, J = 5 Hz) (total 2 H). Anal. $C_{14}H_{20}O_4S$: m/e calcd 284.1081, found 284.1094.

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Registry No.—**10**, 27472-43-1; **11**, 69551-49-1; **12**, 4075-58-5.

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One-Step Synthesis of 1-Oxo-1,2-dihydroisoquinoline-3-carboxylic Acid Derivatives[1]

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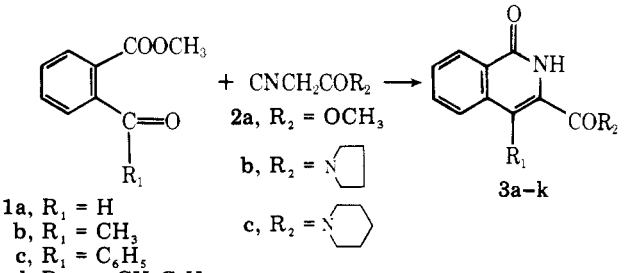
Recently, a number of synthetic studies using isocyanides have been reported and many versatile synthetic methods based on these compounds have been developed.[2] Of these, the reactions of isocyanoacetates with aldehydes or ketones, have been frequently investigated, and a variety of products, e.g., α-*N*-formylaminoacrylates,[3] oxazolines,[4] pyrroles,[5] α-isocyano-β-hydroxybutyrates,[6] and amidines,[7] have been prepared under various reaction conditions.

In the present paper, we wish to report a one-step synthesis of 1-oxo-1,2-dihydroisoquinoline(isocarbostyril)-3-carboxylic acid derivatives by the reaction of methyl 2-acylbenzoates with methyl isocyanoacetate or isocyanoacetamide.

Reaction of methyl isocyanoacetate (**2a**) with methyl 2-formylbenzoate (methyl phthalaldehydate) (**1a**)[8] in the presence of sodium hydride in dimethylformamide at 30–40 °C gave a product whose spectra and melting point showed it to be methyl isocarbostyril-3-carboxylate (**3a**) (Scheme I).[9] To establish the generality of this process, a number of other examples were carried out with both the isocyano ester **2a** and

Scheme I



1a, R_1 = H
b, R_1 = CH_3
c, R_1 = C_6H_5
d, R_1 = p-$CH_3C_6H_4$
e, R_1 = p-$CH_3OC_6H_4$

Scheme II