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Transformations of Resin-Bound Pyridinium Ylides: I. A Stereoselective Synthesis of 2,2,3-Trisubstituted Cyclopropanecarboxylates

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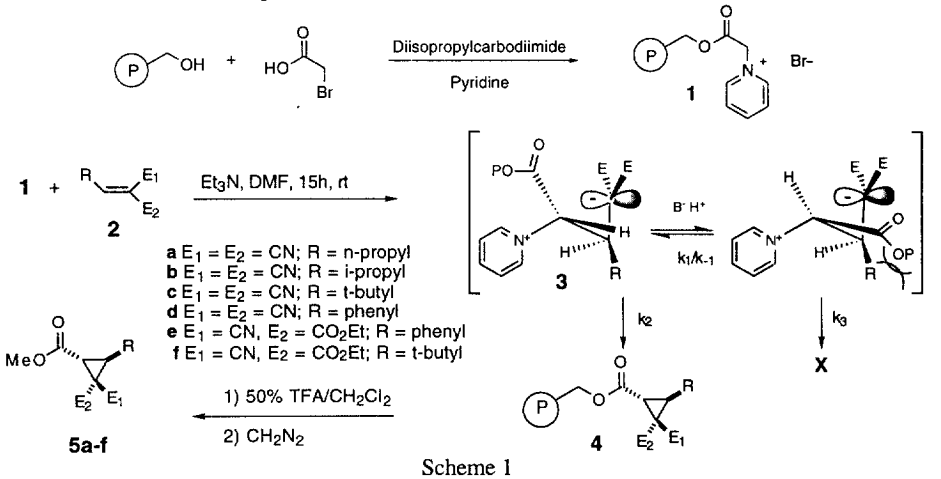
Abstract: Trans-3-alkyl- or -arylcyclopropanecarboxylates, substituted in the 2-position with alkoxycarbonyl or nitrile groups, are efficiently prepared by coupling bromoacetic acid with Wang resin followed by pyridinium ylide formation and condensation of the ylide with ethylidene malonate derivatives. Good yields are obtained after cleaving the resin and esterifying the resulting cyclopropanecarboxylic acid with diazomethane.

In the course of efforts to identify chemical cores with desirable structural and pharmacological properties that are amenable to combinatorial expansion, we have developed a solid-phase synthesis of highly substituted cyclopropanes.[1] Substituted cyclopropanes are ideal scaffolds for exploring determinants of ligand-receptor binding, since the rigid ring orients the substituents into well-defined and spatially isolated trajectories. In this vein, cyclopropanes with defined stereochemistry have been used in several studies as amino acid mimetics with conformationally locked side chains to determine bound peptide conformations.[2] The cyclopropane nucleus is also attractive in that it can be well-tolerated in vivo and does not *a priori* confer undesirable pharmacokinetic properties, as can be seen from the variety of well-established drugs, available for both acute and chronic indications, that contain the group.[3] In this report we describe an efficient procedure for the synthesis of highly substituted cyclopropane intermediates **5a-f** and **8** (Schemes 1 and 2) that can be further elaborated-- on solid support or in solution-- to libraries of potential medicinal value.



Scheme 1

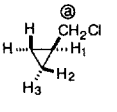
Three previous reports[4, 5, 6] describe solution-phase syntheses of cyclopropanes with substituent patterns analogous to **5a-f**. In one case mixtures of ring isomers were observed;[4] in another the cis isomer was preferred.[5] The use of pyridinium ylides in preparing substituted cyclopropanecarboxamides in solution has been previously noted, although the scope of the reaction has not been fully explored.[6] No references to the solid-phase synthesis of cyclopropanes have appeared.

We find that coupling of bromoacetic acid to Wang resin with excess diisopropylcarbodiimide (DIC) and pyridine provides resin-bound 2-pyridinium acetate **1** (Scheme 1) which is converted readily to the ylide upon treating with trialkylamines. The resulting pyridinium ylide undergoes Michael addition to electron-deficient olefins, followed by intramolecular displacement of pyridine to yield cyclopropanes .

The procedure for synthesis of **5a-f** is most conveniently carried out as follows: **1** is treated with 1.5 equivalent of olefin **2a-f** (the olefins are easily prepared[7] by adding basic alumina to a mixture of aldehyde and malononitrile, ethylcyanoacetic ester, or Meldrum's acid) and 1.5 equivalent of Et_3N in DMF for 15h at room temperature to give resin-bound cyclopropanecarboxylates. The free acids obtained upon routine solid-phase workup (see below) and cleaving the resin are apparently unstable to decarboxylation, and are therefore trapped as methyl esters by treatment with diazomethane. Esters **5a-d** were isolated in 65% to 68% yield as pure compounds (overall yields based on the loading capacity reported by the resin manufacturer). Crude yields were not evaluated due to the instability of the free acids produced, but ^1H NMR of the resin treated with $CDCl_3/CF_3CO_2D$ showed only product resonances, indicating that conversion is reasonably complete and that the method should be applicable to library synthesis. Although two diastereomers are possible, only the *trans* diastereomer between C1 and C3 is observed in each case. This selectivity is presumably due to ready epimizeration of the pyridinium-substitued carbon and fast cyclization of the anti adduct (**3**, Scheme 1) relative to the syn adduct- that is, k_1, k_{-1} and k_2 are all faster than k_3. This mechanism was proposed to explain the observation that, in solution, some stereoselectivity occurs in the Michael reaction with ethylidenemalononitrile, but both syn and anti Michael adduct cyclize to yield *trans* cyclopropane[6].

When E_1 and E_2 are different (**2e-f**), a secondary stereoselective reaction can occur. When R is a phenyl group a 4:1 mixture of **5e** was obtained in 69% yield. NOE experiments indicated that both isomers of **5e** are trans at C1 and C3. The major isomer of **5e** is tentatively assigned as the isomer having the cyano group syn to the phenyl group. A single diastereomer **5f** (82%) is obtained when R is a more bulky *tert*-butyl group. This selectivity suggests that the less sterically demanding cyano group is syn to the R group. The relative stereochemistry of **5f** was established by determination of 3-bond carbon-proton coupling constants. Based on the model compound, chloromethyl cyclopropane (**6**) establishes that the coupling between the chloromethylene carbon and the trans ring proton (H_3) is 3.5 Hz, while the coupling with the cis ring proton (H_2) is 6.6 Hz. A similar experiment was carried out for **5f**. A small coupling constant (2.9 Hz) between the ethyl ester carbon (C_a) and H_1 proton suggested a trans orientation between these nuclei, while a larger coupling (5.1 Hz) with H_3 established a cis orientation. Analogously, the coupling constants between the cyano carbon (C_b) with H_1 and with H_3 are 6.1 Hz and 4.3 Hz respectively. These coupling constants support the proposed structure for **5f**:

$^3J_{a,3} = 3.5$ Hz
$^3J_{a,2} = 6.6$ Hz
$^2J_{a,1} = 0.0$ Hz



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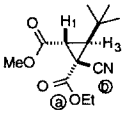


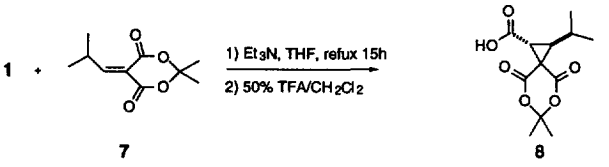
5f

$^3J_{a,1} = 2.9$ Hz
$^3J_{a,3} = 5.1$ Hz

$^3J_{b,1} = 6.1$ Hz
$^3J_{b,3} = 4.3$ Hz

Under several conditions benzylidene-diethylmalonate yields a complex mixture of products on reaction with **1**. Meldrum's acid derivative **7** reacts sluggishly at room temperature (Scheme 2). The diester functionality was finally introduced by carrying out the reaction at elevated temperature in THF; a 79% yield of **8** was

obtained after cleavage. It is noteworthy that unlike **5a-e**, **8** is stable and can be isolated as a free acid. Pyridinium **1** failed to react with monoactivated olefins under the conditions described .



7 8

Scheme 2

In cases where at least one of the E groups is a keto or a nitro group, a different mode of cyclization occurs to yield dihydrofurans and isoxazoline N-oxides respectively. We will disclose further details regarding these alternate modes of cyclization in due course.

EXPERIMENTAL PROCEDURES

General: All compounds gave satisfactory spectral and elemental analyses[8]. Wang resin was purchased from Advanced ChemTech (Louisville, KY 40228) and used without further purification.

Preparation of pyridinium acetate 1: Into a suspension of Wang resin (10.0g, 8.50 mmol) in dichloromethane (80 mL) at 0 °C were added bromoacetic acid (5.92g, 42.6 mmol), DIC (5.36g, 42.6 mmol) and pyridine (3.36g, 42.6 mmol). After 15 min at 0 °C, the mixture was shaken at rt for 2h. The resin was filtered and retreated to the above conditions with extra pyridine (6.72g, 85.2 mmol) and shaken at room temperature overnight. The resin suspension was filtered and washed with 2-propanol and dichloromethane (repeated five times), then dried by air suction. A light yellow resin (10.98g) was obtained.

General procedure for preparation of cyclopropanes. Into a suspension of the pyridinium-bound resin (500mg, est. 0.39 mmol) in DMF (4 mL) were added olefin **2** (0.59 mmol) and Et_3N (60 mg, 0.59 mmol). The mixture was shaken at rt overnight, filtered, washed with 2-propanol and dichloromethane (repeated five times) and dried by air suction. The dried resin was treated with a 50% solution of trifluoroacetic acid in dichloromethane (5 mL) and triethylsilane (5 drops). The suspension was shaken at rt for 2 h and filtered. The filtrate was collected and concentrated under a stream of N_2. The crude mixture was treated with a solution of CH_2N_2 in ether. Excess CH_2N_2 was quenched by addition of HOAc. The solvents were removed under reduced pressure. The crude residue was purified on silica (2:8, EtOAc : hexanes) to give the products (65% to 82%, based on the manufacturer's reported loading capacity of the Wang resin).

The reaction with Meldrum's acid derivative did not work well under the above conditions. Incomplete reaction was observed. By carrying the reaction in THF at reflux overnight, a 79% yield of carboxylic acid **8** was obtained after cleavage. This cyclopropylcarboxylate is stable and can be purified by simple filtration on silica (1:99 HOAc : Ether). The reaction can be monitored by removing 10 to 20 mg of resin from the reaction mixture. After washing and drying as usual, the resin is placed in an NMR tube with 50% d-TFA in $CDCl_3$ for 30 min. ^1H NMR then allows the determination of the extent of reaction.

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8 **5a:** ^{1}H NMR 3.84 (s, 3), 2.46 (d, 1, J = 8.0), 2.40 (dt, 1, J = 8.0, 7.7), 1.72-1.55 (m, 4), 1.01 (t, 3, J = 7.2); ^{13}C NMR 165.70, 112.30, 111.77, 53.45, 35.30, 34.64, 30.65, 21.09, 13.36, 11.40; IR (neat) 3056, 2251, 1744. MS (ES): m/z 193 (M + H$^+$). HRMS: calcd for $C_{10}H_{13}N_2O_2$ 193.0977, found 193.0978. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.35; H, 6.06; N, 14.18. **5b:** (m.p. 79-80 °C); ^{1}H NMR 3.84 (s, 3), 2.50 (d, 1, J = 7.7), 2.22 (dd, 1, J = 10.6, 7.7), 1.51 (dh, 1, J = 10.6, 6.6), 1.23 (d, 3, J = 6.6), 1.15 (d, 3, J = 6.6); ^{13}C NMR 165.64, 112.30, 111.70, 53.46, 41.70, 35.15, 30.08, 21.03, 20.83, 11.28; IR (neat) 3060, 3036, 2249, 1736. MS (ES): m/z 193 (M + H$^+$). HRMS: calcd for $C_{10}H_{13}N_2O_2$ 193.0977, found 193.0981. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.38; H, 6.14; N, 14.33. **5c:** (m.p. 89-90 °C); ^{1}H NMR 3.83 (s, 3), 2.70 (d, 1, J = 8.8), 2.30 (d, 1, J = 8.8), 1.12 (s, 9); ^{13}C NMR165.93, 112.77, 112.25, 53.49, 45.36, 32.44, 30.50, 27.95, 8.92; IR (neat) 3057, 2249, 1743. MS (ES): m/z 207 (M + H$^+$). HRMS: calcd for $C_{11}H_{15}N_2O_2$ 207.1134, found 207.1132. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.27; H, 6.82; N, 13.28. **5d:** (m.p. 98-99 °C); ^{1}H NMR 7.46-7.40 (m, 3), 7.33-7.28 (m, 2), 3.91 (s, 3), 3.69 (d, 1, J = 8.1), 3.17 (d, 1, J = 8.1); ^{13}C NMR 165.45, 129.88, 129.29, 128.88, 128.25, 111.61 (2 C), 53.75, 38.49, 33.38, 13.96; IR (neat) 3062, 2250, 1742. MS (ES): m/z 227 (M + H$^+$). HRMS: calcd for $C_{13}H_{11}N_2O_2$ 227.0821, found 227.0831. Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.47; N, 12.38. Found: C, 68.73; H, 4.55; N, 12.28. **5e** (4:1 cis-trans mixture): ^{1}H NMR 7.46-7.25 (m, 5), 4.37 (dq, 0.8, J = 10.8, 7.3), 4.32 (dq, 0.8, J = 10.8, 7.0), 4.05 (q, 0.2, J = 7.1), 3.71 (s, 3 X 0.2), 3.81 (s, 3 X 0.8), 3.76 (d, 0.2, J = 8.0), 3.69 (d, 0.8, J = 8.5), 3.42 (d, 0.2, J = 8.0), 3.14 (d, 0.8, J = 8.5), 1.38 (dd, 3 X 0.8, J = 7.3, 7.0), 1.08 (t, 3 X 0.2, J = 7.1); ^{13}C NMR (both) 167.27, 165.85, 164.03, 162.31, 131.41, 130.27, 128.92, 128.89, 128.54, 128.16, 115.11, 114.88, 63.54, 63.25, 53.11, 52.97, 39.58, 36.61, 35.44, 31.74, 28.35, 13.97, 13.74; IR (neat, both) 3063, 3030, 2248, 1739. MS (NH$_3$-CI): m/z 291 (M + NH$_4^+$). HRMS: calcd for $C_{15}H_{16}N_1O_4$ 274.1079, found 274.1082. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.14. Found: C, 65.98; H, 5.63; N, 5.16. **5f:** (m.p. 82-83 °C); ^{1}H NMR 4.27 (dq, 1, J = 10.8, 7.0), 4.23 (dq, 1, J = 10.8, 7.3), 3.72 (s, 3), 2.67 (d, 1, J = 8.8), 2.34 (d, 1, J = 8.8), 1.33 (dd, 3, J = 7.3, 7.0), 1.14 (s, 9); ^{13}C NMR 166.62, 164.76, 116.24, 63.27, 52.68, 43.32, 34.17, 29.99, 28.00, 23.02, 13.89; IR (neat) 3025, 2240, 1740, 1725. MS (NH$_3$-CI): m/z 271 (M + NH$_4^+$). HRMS: calcd for $C_{13}H_{20}N_1O_4$ 254.1392, found 254.1386. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.54. Found: C, 61.77; H, 7.22; N, 5.34. **8** (containing trace amount of epimeric product): (m.p. 155-157°C) ^{1}H NMR 3.09 (d, 1, J = 9.2), 2.58 (dd, 1, J =10, 9.2), 2.08 (dqq, 1, J = 10, 6.9, 6.6), 1.83 (bs, 6), 1.16 (d, 3, J = 6.9), 0.98 (d, 3, J = 6.6); (minor epimer) 3.20 (d, 1, J = 9.9), 2.30 (dd, 1, J = 9.9, 10), 1.22(d, 3, J = 6.6), 0.95 (d, 3, J = 7); ^{13}C NMR 170.92, 165.74, 164.58, 105.63, 48.93, 41.04, 33.82, 27.83, 27.79, 25.95, 21.65; IR (neat) 1769, 1744, 1720. MS (NH$_3$-CI): m/z 274 (M + NH$_4^+$). HRMS: calcd for $C_{12}H_{17}O_6$ 257.1025, found 257.1037. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.38; H, 6.20.

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