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REACTION OF TRIFLUOROMETHANESULFONYL CHLORIDE WITH DIALKYL HYDROXYALKYLMALONATES. A SYNTHESIS OF 2,2-DISUBSTITUTED TETRAHYDROFURANS, PYRANS AND PYRROLIDINES.

Gholam Hosein Hakimelahi and George Just*
Department of Chemistry, McGill University, 801 Sherbrooke St. West,
Montreal, PQ, Canada H3A 2K6.

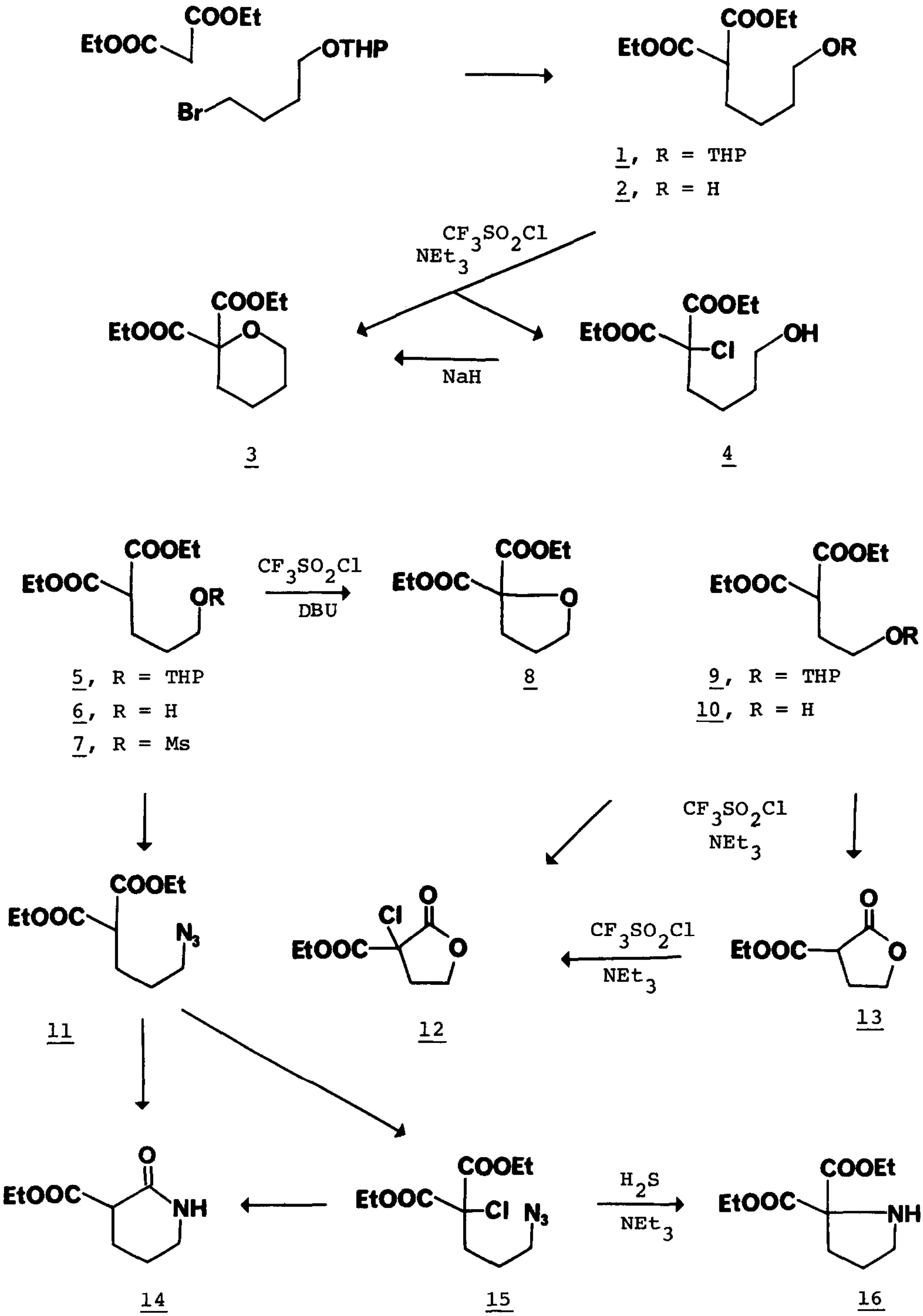
Diethyl 2-(ω-hydroxypropyl or butyl) malonates are shown to give 2,2-dicarbethoxytetrahydrofuran or tetrahydropyran, when allowed to react with CF_3SO_2Cl/NEt_3 in CH_2Cl_2.

In the preceding paper,[1] we described the selective chlorinating action of CF_3SO_2Cl on carbanions stable enough to be formed by NEt_3 or DBU in methylene chloride, and the relative speed of this reaction versus the well-known sulfonation of alcohols (k chlorination/k sulfonation $\geq 10^5$). In this communication, we would like to demonstrate the usefulness of this reaction in forming oxygen heterocycles, and, less directly, nitrogen heterocycles.

Diethyl malonate was monoalkylated[2] with 1-bromo-4-tetrahydropyranyloxybutane. Distillation of the crude tetrahydropyranyl ether 1 gave alcohol 2.[3,4] Treatment of 2 (1 mmole) with CF_3SO_2Cl (1 mmole) and NEt_3 (2 mmole) in CH_2Cl_2 (15 ml) at room temperature for 3 hr gave a 50:50 mixture of pyran 3[5] and chloroalcohol 4.[3,6] The latter could be converted to pyran 3 by the action of NaH (1 eq) in THF.

Monoalkylation of diethylmalonate with 1-bromo-3-tetrahydropyranyloxypropane as described gave tetrahydropyranyl ether 5,[3,7] which was transformed to alcohol 6[3,8] by treating it with pyridinium tosylate in ethanol.[9] Reactions of 6 (1 mmole) with CF_3SO_2Cl (1 mmole) and DBU (2 mmole) in methylene chloride at 22° for 3 hr gave a quantitative yield of 2,2-dicarbethoxyfuran (8).[10]

Monoalkylation of diethylmalonate with 1-bromo-2-tetrahydropyranyloxyethane gave ether 9,[3] which was transformed to alcohol 10[3,11] with pyridinium tosylate.[9] Hydroxyester 10 lactonized spontaneously within 5 - 10 hr to give lactone 13.[3,12] Treatment of either lactone 13 or hydroxyester 10 with


1, R = THP
2, R = H
CF3SO2Cl
NEt3
NaH
3
4
CF3SO2Cl
DBU
5, R = THP
6, R = H
7, R = Ms
8
9, R = THP
10, R = H
CF3SO2Cl
NEt3
CF3SO2Cl
NEt3
11
12
13
H2S
NEt3
14
15
16

CF_3SO_2Cl/NEt_3 in CH_2Cl_2 at 20° for 1 hr gave a quantitative yield of chlorolactone 12,[3,13] indicating that, as could have been expected, lactonization to form a five-membered ring proceeded more rapidly than the formation of a four-membered ether.

It seemed logical to try to extend this methodology to the formation of nitrogen heterocycles. Alcohol 6 was transformed to its mesylate 7,[3] and the mesylate function displaced by azide to give azidoester 11.[3,14] Catalytic reduction of 11 resulted in reduction of the azide function and spontaneous formation of valerolactam 14.[3,15] Since it proved impossible to form the free amine (11, $N_3 = NH_2$), we next treated azide 11 with CF_3SO_2Cl/NEt_3 and obtained chloroazide 15.[3,16] Catalytic reduction gave diethyl 3-aminopropylmalonate hydrochloride, which upon neutralization with aqueous $NaHCO_3$ formed 2-carbethoxyvalerolactam 14[3,15] spontaneously. However, when the reduction of chloroazide 15 was carried out with H_2S/Et_3N,[17] a quantitative yield of 2,2-dicarbethoxypyrrolidine 16[18] was obtained.

When the latter sequence 11 → 15 → 16 was repeated with diethyl 4-azidobutylmalonate - the higher homologue of 11, - no piperidine analogous to 16 was isolated. Instead, lactam formation was observed and 2-carbethoxy-2-chlorocaprolactam[3,19] was obtained.

The ring-closure reactions observed may well be the result of an S_N2-displacement, although other mechanisms cannot be ruled out at the present time.

Furans 3 and 8, and lactone 12

To alcohols 2, 6 or 10 (1 mmole) in 15 ml CH_2Cl_2 containing 2 mmol NEt_3 (or DBU) was added at 20-25° CF_3SO_2Cl (1 mmole) in 5 ml CH_2Cl_2 dropwise over a period of a few minutes with stirring. After 3 hr, the solution was washed with water and dried ($MgSO_4$). Chromatography over silica gel using CH_2Cl_2 as eluent gave 3, 8 or 12 respectively in 50, >95 and >95% yield.

Acknowledgements

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References and footnotes

1. G.H. Hakimelahi and G. Just, Tet. Lett.,3643(1979).
2. N. Weiner, Organic Syntheses, Coll. Vol. 2, 279, A.H. Blatt ed., John Wiley and Sons, New York, 1950.

3. P.m.r. spectrum compatible with structure proposed.
4. 2: b.p. 170-1°/10 mm Hg, C.I. m/e 233 ($C_{11}H_{20}O_5$+1), 215 ($M^+ + 1 - H_2O$), 187 (M^+ - OEt).
5. 3: δ 1.35 (6H, t, J = 7 Hz, $\underline{H}_3CCH_2O$), 1.4 - 2.4 (6H, broad), 3.58 (2H, t, J = 7Hz, $CH_2C\underline{H}_2O$), 4.3 ppm (4H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); C.I. m/e 231 (M^+ + 1), 157 (M^+ - COOEt); calcd. for $C_{11}H_{18}O_5$ C 57.38 H 7.88 found C 57.40 H 8.10.
6. 4: C.I.m/e 249 ($C_{11}H_{19}ClO_5 + 1 - H_2O$, Cl - cluster), 221 ($M^+$ - OEt, Cl cluster).
7. 5: C.I.m/e 219 ($C_{15}H_{26}O_6$ (302) + 1 - dihydropyran), 201 (219 - H_2O), 173 (M^+ - dihydropyran - OEt).
8. 6: C.I.m/e 219 (M^+ + 1), 201 ($M^+ + 1 - H_2O$), 173 (M^+ - OEt).
9. M. Miyashita, A. Yoshikoshi and P.A. Grieco, J. Org. Chem. 42, 3772 (1977).
10. 8: ν 1745 cm^{-1}, δ 1.35 (6H, t, J = 7 Hz, $\underline{H}_3CCH_2O$), 1.8 - 2.2 (2H, m), 2.2 - 2.6 (2H, m), 3.62 (2H, t, J = 6 Hz, $CH_2C\underline{H}_2O$), 4.3 ppm (4H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); C.I.m/e 217 (M^+ + 1), 171 (M^+ - OEt), 143 (M^+ - COOEt); calcd. for $C_{10}H_{16}O_5$ C 55.54 H 7.46, found C 55.30 H 7.22.
11. 10: C.I.m/e 205 ($C_9H_{16}O_5$ + 1), 187 ($M^+ + 1 - H_2O$), 159 (M^+ - OEt).
12. 13: ν 1780, 1740 cm^{-1}, C.I.m/e 159 (M^+ + 1).
13. 12: ν 1790, 1760, 1740 cm^{-1}, C.I.m/e 193 (M^+ + 1, Cl cluster).
14. 11: ν 2100, 1745 cm^{-1}, C.I m/e 244 (M^+ + 1), 216 ($M^+ + 1 - N_2$), 201 ($M^+ - N_3$), 170 (M^+ - COOEt).
15. 14: ν 3400 (NH), 1730 (COOEt), 1670 (CONH), C.I.m/e 172 (M^+ + 1).
16. 15: ν 2100, 1745 cm^{-1}, C.I.m/e 278 (M^+ + 1, Cl-cluster), 250 ($M^+ + 1 - N_2$, Cl-cluster).
17. T.W. Doyle, B. Belleau, B.Y. Luh, C.F. Ferrari and M.P. Cunningham, Can. J. Chem. 55, 468 (1977).
18. 16: ν 3300, 1745 cm^{-1}, δ 1.32 (6H, t, J = 7 Hz, $C\underline{H}_3CH_2O$), 1.7 - 2.1 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.2 - 2.38 (2H, m, $C\underline{H}_2CH_2CH_2NH$), 3.38 (2H, t, J = 6.8 Hz, $C\underline{H}_2NH$), 4.3 ppm (4H, q, J = 7 Hz, $CH_3C\underline{H}_2O$). C.I.m/e 216 (M^+ + 1), 142 (M^+ - COOEt); calcd. for $C_{10}H_{17}NO_4$ C 55.80 H 7.96 N 6.51 found C 56.12 H 7.81 N 6.29.
19. 2-Carbethoxy-2-chlorocaprolactam: ν 3200, 1740, 1630 cm^{-1}, C.I. m/e 220 (M^+ + 1, Cl-cluster), 174 (M^+ - OEt, Cl-cluster).

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