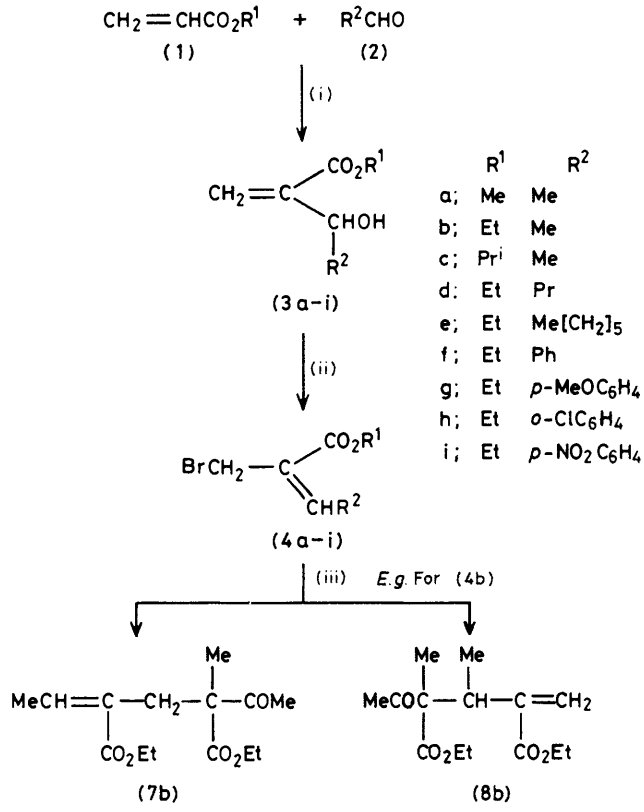
# Necic Acid Synthons. Part 2.[1] Regioselectivity in the Reactions of (*Z*)-2-Bromomethyl-2-alkenoate Esters with Selected Carbon Nucleophiles

**Farouk Ameer, Siegfried E. Drewes,* Neville D. Emslie, Perry T. Kaye, and R. Leigh Mann**
*Department of Chemistry, University of Natal, Pietermaritzburg, South Africa*

The preparation of selected (*Z*)-2-bromomethyl-2-alkenoate esters and their subsequent reaction with acetoacetic ester-derived nucleophiles is described. Both the substrate structure and the solvent system have significant effects on the regioselectivity of these nucleophilic displacements.

During the past few years there has been renewed interest in the preparation of necic acids [2,3] and the development of a convenient ' general synthesis,' sufficiently versatile to afford closely related natural systems, as well as specific synthetic analogues, would be invaluable. Our interest in these compounds stems from a continuing study of *Senecio* alkaloids [4,5] and includes a recent description of the total synthesis of integerrinecic acid *via* ethyl 3-acetoxy-2-methylenebutanoate.[1]† We now report the results of regioselectivity studies which clearly illustrate the potential of the title compounds as necic acid synthons.

*Bromination Studies.*—Goldberg and Dreiding [6] have obtained the (*Z*)-bromo ester (4b) by treating the hydroxy ester (3b) with NBS–$Me_2S$.[7]‡ We have found that reaction of the same hydroxy ester (3b) with conc. HBr–conc. $H_2SO_4$ [8] at room temperature is a more convenient route to the bromo ester (4b) and have shown this product and the derived bromo acid to be identical ($^1H$ and $^{13}C$ n.m.r. and i.r. spectroscopy) with the compounds obtained by Goldberg and Dreiding's method.[6] The series of *rearranged* (*Z*)-bromo esters (4a—i) was consequently prepared by treating the corresponding hydroxy esters (3a—i) [9] with conc. HBr–conc. $H_2SO_4$ (Scheme). Assignment of the *Z* configuration to the rearranged bromo esters used in this study is based on the assumption that the allylic C(3′) $^{13}C$ chemical shift for a (*Z*)-isomer will be at higher field than the corresponding signal for its (*E*)-isomer.[10] The C(3′) $^{13}C$ signals for two esters isomeric with compounds (4b) and (4c), respectively,§ appear at δ 36.5 ± 0.1 p.p.m. whereas the corresponding signals for compounds (4a, b, c, d, f, and i) appear at δ 25.1 ± 1.5 p.p.m. Comparison of the $^1H$ and $^{13}C$ n.m.r. spectra for the esters (4b) and (4c) and their respective geometric isomers indicate that the vinylic proton shifts [11] and $J_{H\text{-}C(3)/C(3')}$ coupling constants [6] are unsuitable configurational criteria in this series.

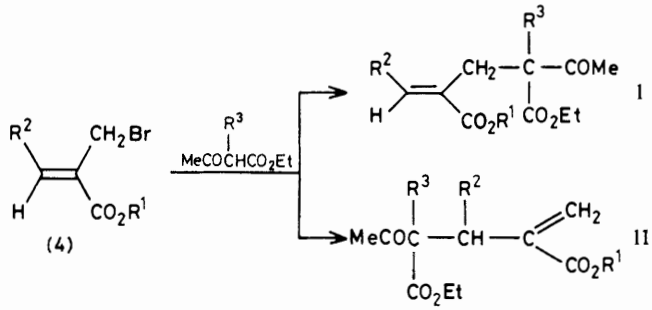



**Scheme.** Outline of overall reaction showing possible variations of substituents. *Reagents:* (i) 1,4-Diazabicyclo[2.2.2]octane, room temp.; (ii) conc. HBr–conc. $H_2SO_4$; (iii) MeCOCH(Me)$CO_2$Et–NaH–THF *or* MeCOCH(Me)$CO_2$Et–NaOEt–EtOH

*Regioselectivity Studies.*—Allylic halides commonly undergo nucleophilic displacement with and without concomitant rearrangement,[12] and 2-bromomethyl-2-alkenoate esters may be expected to react similarly. In most of the examples studied both substitution modes are, in fact, observed. The two product types, *normal* and *rearranged* (arising from *allylic* and *vinylic* attack, respectively), may be readily distinguished by means of their $^1H$ n.m.r. vinylic-hydrogen signals, and the product distributions estimated from the relative integrals. Eight different substrates have been examined under various conditions and the results of these studies are summarised in Table 1. Variation of the substrate substituents [$R^1$, $R^2$ (Figure 1)], the nature of the nucleophile, and the base–solvent system all influence the product distribution, and judicious choice of these variants permits significant regiocontrol. Thus, for ethyl (*Z*)-2-bromomethylbut-2-enoate (4b), the distribution may be shifted in favour of the *normal* or the *rearranged* product simply by changing the base–solvent system (Scheme). The fact that the products (7b) and (8b) are suitable precursors for integerrinecic and sceleranecic acid, respectively, emphasises the synthetic utility of these reactions.

† Ethyl 2-(1-acetoxyethyl)prop-2-enoate.
‡ NBS is *N*-bromosuccinimide.
§ The synthesis of esters in the isomeric series forms part of a continuing study, the results of which will be published in due course. Data [compound, *H*–C(3) and C(3′) chemical shift (δ/p.p.m.), and $J_{H\text{-}C(3)/C(3')}$ coupling constant (Hz)] relevant to the present discussion are: ethyl ester isomeric with (4b), 7.06 and 36.48, 9.3; and isopropyl ester isomeric with (4c), 7.05 and 36.63, 9.1.

**Table 1.** Percentage relative distribution between *normal* (I) and *rearranged* (II) products in the reaction




| Substrate | $R^1$ | $R^2$ | Base–solvent system | Relative product-distribution I : II (%) [a] $R^3$ = H I (5) | II (6) | $R^3$ = Me I (7) | II (8) | $R^3$ = $PhCH_2$ I (9) | II (10) |
|---|---|---|---|---|---|---|---|---|---|
| (4a) | Me | Me | NaH–THF [b] | 17 | 83 | | | | |
| | | | NaOEt–EtOH | 80 | 20 | | | | |
| (4b) | Et | Me | NaH–THF | 32 | 68 | 30 | 70 | | |
| | | | NaOEt–EtOH | 72 | 28 | 100 | 0 | | |
| (4d) | Et | $CH_3[CH_2]_2$ | NaH–THF | 50 | 50 | 65 | 35 | | |
| | | | NaOEt–EtOH | 85 | 15 | 100 | 0 | | |
| (4e) | Et | $CH_3[CH_2]_5$ | NaH–THF | 47 | 53 | 63 | 37 | 80 | 20 |
| | | | NaOEt–EtOH | 85 | 15 | 100 | 0 | 100 | 0 |
| (4f) | Et | Ph | NaH–THF | 50 | 50 | 88 | 12 | 100 | 0 |
| | | | NaOEt–EtOH | 90 | 10 | 100 | 0 | 100 | 0 |
| (4g) | Et | *p*-$MeOC_6H_4$ | NaH–THF | 80 | 20 | 100 | 0 | | |
| | | | NaOEt–EtOH | 100 | 0 | 100 | 0 | | |
| (4h) | Et | *o*-$ClC_6H_4$ | NaH–THF | 76 | 24 | 100 | 0 | | |
| | | | NaOEt–EtOH | 100 | 0 | 100 | 0 | | |
| (4i) | Et | *p*-$NO_2C_6H_4$ | NaH–THF | 34 | 66 | 77 | 23 | | |
| | | | NaOEt–EtOH | 100 | 0 | 100 | 0 | | |

[a] Determined by $^1H$ n.m.r. spectroscopy of reaction mixture after work-up. [b] THF = tetrahydrofuran.

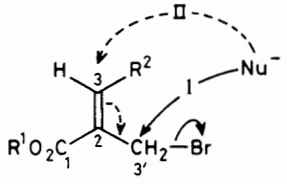



**Figure 1.** I: *Allylic* attack affording *normal* product. II: *Vinylic* attack affording *rearranged* product

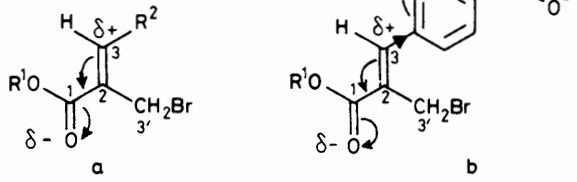



**Figure 2.** Effect of substituents on nucleophilic attack on vinylic carbon

Examination of the product distribution (Table 1) reveals certain significant trends. Thus, nucleophilic attack at the *allylic* carbon [C(3′), Figure 1] is enhanced by (i) changing the base-solvent system from NaH–THF to NaOEt–EtOH; (ii) increasing the steric bulk of the nucleophile ($R^3$ = H ⟶ Me ⟶ $PhCH_2$) [the small discrepancy observed for substrate (4b) (NaH–THF) being anomalous]; (iii) varying the alkyl substituents $R^2$ [from methyl (4b) to propyl (4d) or hexyl (4e)] *or* $R^1$ [from methyl (4a) to ethyl (4b)]; and (iv) introducing aryl groups [Ph (4f), *p*-$MeOC_6H_4$ (4g), or *o*-$ClC_6H_4$ (4h) *but not* *p*-$NO_2C_6H_4$ (4i)] as substituent $R^2$.

These trends may be tentatively accommodated by assuming (i) significant *bimolecular* displacement in the less polar solvent THF, favouring nucleophilic attack at the relatively electrophilic and accessible $sp^2$ *vinylic* carbon C(3) (Figure 2a), and (ii) significant *unimolecular allylic* displacement in the more polar EtOH. Preferential attack at the primary *allylic* carbon C(3′) in the latter ($S_N1$) case may be rationalised from a consideration of steric effects and the *natural product spread*.[13] The importance of *allylic* substitution in the aryl systems (4f), (4g), and (4h) may be attributed to the consequent retention of extended conjugation while the anomalous trends noted for the *p*-nitrophenyl derivative (4i) presumably reflect additional enhancement of the electrophilicity of the *vinylic* carbon by the strongly electron-withdrawing *p*-nitrophenyl substituent (Figure 2b).

## Experimental

$^1H$ and $^{13}C$ N.m.r. spectra were obtained from $CDCl_3$ solutions on Varian T60 or Varian FT80A n.m.r. spectrometers, using

**Table 2.** Characterisation of new compounds

| Compound (Molecular formula) | M.p. (°C) or B.p. (°C/mmHg) | Found (%) (Required) C | H |
|---|---|---|---|
| (4d) | 85—90/2.5 | 45.8 | 6.3 |
| ($C_9H_{15}BrO_2$) | | (46.0 | 6.4) |
| (4g) | 155—165/1 | 52.3 | 5.1 |
| ($C_{13}H_{15}BrO_3$) | | (52.2 | 5.05) |
| (4h) | 142—147/5 | 47.8 | 4.0 |
| ($C_{12}H_{12}BrClO_2$) | | (47.5 | 4.0) |
| (4i) | 99 | 45.8 | 3.9 |
| ($C_{12}H_{12}BrNO_4$) | | (45.9 | 3.9) |
| (5a) | 98—102/19 | 59.6 | 7.6 |
| ($C_{12}H_{18}O_5$) | | (59.5 | 7.5) |
| (6a) | 164—166/46 | 59.6 | 7.5 |
| ($C_{12}H_{18}O_5$) | | (59.5 | 7.5) |
| (7e) | 160—172/5 | 67.1 | 9.5 |
| ($C_{19}H_{32}O_5$) | | (67.0 | 9.5) |
| (9e) | — | 72.2 | 8.5 |
| ($C_{25}H_{36}O_5$) | | (72.1 | 8.7) |
| (5f) | 208—212/3 | 68.0 | 7.0 |
| ($C_{18}H_{22}O_5$) | | (67.9 | 7.0) |
| (7f) | 165—175/4 | 69.05 | 7.2 |
| ($C_{19}H_{24}O_5$) | | (68.7 | 7.3) |
| (9f) | 210—215/2 | 73.2 | 6.6 |
| ($C_{25}H_{28}O_5$) | | (73.5 | 6.9) |
| (5g) | 154–160/2.5 | 65.4 | 7.0 |
| ($C_{19}H_{24}O_6$) | | (65.5 | 6.9) |
| (7g) | 168—178/2.5 | 66.5 | 7.1 |
| ($C_{20}H_{26}O_6$) | | (66.3 | 7.2) |
| (5h) | 43 | 61.3 | 6.0 |
| ($C_{18}H_{21}ClO_5$) | | (61.3 | 6.0) |
| (7h) | 148—154/2 | 62.4 | 5.8 |
| ($C_{19}H_{23}ClO_5$) | | (62.2 | 6.3) |

$SiMe_4$ as reference standard. Analytical data for new compounds are given in Table 2. H.p.l.c. (high-performance liquid chromatography) separations were effected on a Waters preparative LC/System 500A chromatograph.

*Bromination of the 3-Hydroxy-2-methylenealkanoate Esters.*—Compounds (3a—i) [obtained from the corresponding acrylate esters (1) and aldehydes (2)] were prepared as illustrated by the following example.

*Ethyl (Z)-2-bromomethylbut-2-enoate* (4b). *Method A.* Conc. HBr (48%; 110 ml) and then conc. $H_2SO_4$ (100 ml) were added dropwise to stirred ethyl 2-(1-hydroxyethyl)propenoate (3b) (50 g, 0.347 mol) at *ca.* 25 °C. After being stirred overnight the mixture was extracted with $Et_2O$. The combined extracts were dried ($Na_2SO_4$) and the solvent was evaporated under reduced pressure. The residual oil was distilled to give ethyl (*Z*)-2-bromomethylbut-2-enoate (4b) (52.4 g, 73%).

*Method B.* The hydroxy ester (3b) was treated with NBS–$Me_2S$ in $CH_2Cl_2$ as described by Goldberg and Dreiding [6] to give the required bromo derivative (4b) in 58% yield.

*Regioselectivity Studies.*—The reported product-distributions were estimated from $^1H$ n.m.r. spectra of the reaction mixtures in $CDCl_3$, obtained on a Varian T60 n.m.r. spectrometer. The general procedures for the transformations summarised in Table 1 are illustrated by the reactions of methyl 2-bromomethylbut-2-enoate (4a) with ethyl acetoacetate.

*Method A.* A solution of ethyl acetoacetate (3.58 g) in dry THF (50 ml) was added dropwise to a stirred suspension of NaH (80% dispersion in oil; 0.825 g) in dry THF (50 ml) under dry $N_2$ and the resulting mixture was stirred for 1 h. Methyl 2-bromomethylbut-2-enoate (4a) (5 g) was then added dropwise and the mixture was stirred for a further 3 h. The reaction was quenched with water and the mixture was extracted with $Et_2O$. The extract was dried (anhydrous $MgSO_4$) and evaporated to give an oil (5 g) [containing the isomeric products (5a) (17%) and (6a) (83%)] from which the major product (6a) was isolated by distillation and preparative g.l.c.

*Method B.* Sodium wire (0.72 g) was added to a solution o ethyl acetoacetate (4.03 g) in dry EtOH (50 ml) under dry $N_2$. Methyl 2-bromomethylbut-2-enoate (4a) (5.8 g) was added dropwise to this (cooled) solution and the resulting mixture was stirred for 3 h. Work-up, as described for Method A, gave an oil (4.9 g) [containing the isomeric products (5a) (80%) and (6a) (20%)] from which the major product (5a) was isolated by distillation and preparative g.l.c.

Analytical data for new compounds isolated in the regioselectivity study are summarised in Table 2. The remaining new compounds were not isolated but were identified, by analogy, from $^1H$ n.m.r. spectra of the reaction mixtures obtained after work-up.

## Acknowledgements

The authors thank the South African Council for Scientific and Industrial Research and the University of Natal Research Fund for financial support.

## References

1 S. E. Drewes and N. D. Emslie, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2079.
2 C. G. Gordon-Gray and C. G. Whiteley, *J. Chem. Soc., Perkin Trans. 1*, 1977, 2040.
3 U. Pastewka, H. Wiedenfeld, and E. Röder, *Arch. Pharm. (Weinheim, Ger.)*, 1980, **313**, 846.
4 S. E. Drewes, I. Antonowitz, P. T. Kaye, and P. C. Coleman, *J. Chem. Soc., Perkin Trans. 1*, 1981, 287.
5 S. E. Drewes and A. T. Pitchford, *J. Chem. Soc., Perkin Trans. 1*, 1981, 408.
6 O. Goldberg and A. S. Dreiding, *Helv. Chim. Acta*, 1976, **59**, 1904.
7 E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Lett.*, 1972, 4339.
8 M. Kaeriyama, T. Sato, S. Hashimoto, M. Mizuno, M. Ando, and H. Yoneda, Jap.P. 7 695 016/August 1976 (*Chem. Abstr.*, 1976, **85**, 176872e).
9 A. B. Baylis and M. E. Hillman, Ger. Offen. 2 155 113/May 1972 (*Chem. Abstr.*, 1972, **77**, 34174q).
10 See reference 3 and N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, 1974, **8**, 1.
11 U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, 1969, **25**, 691.
12 R. M. Magid, *Tetrahedron*, 1980, **36**, 1901; R. H. de Wolfe and W. G. Young, *Chem. Rev.*, 1956, **56**, 753.
13 J. March, 'Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,' McGraw-Hill, New York, 1977, 2nd edn., p. 304.

*Received* 29*th December* 1982; *Paper* 2/2168