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REGIOSPECIFIC SYNTHESIS OF (E) UNSATURATED 3,5-DIALKYL-ISOXAZOLES AND DERIVED LEUKOTRIENE ANALOGUES USING PHOSPHINE OXIDES

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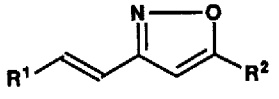
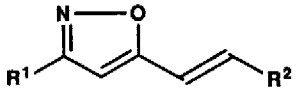
Isoxazoles with 3-alkyl and 5-E-alkenyl substituents and vice-versa can be made regiospecifically from phosphine oxides by the Horner-Wittig reaction. The isoxazole ring in the products is cleaved by $Mo(CO)_6$.

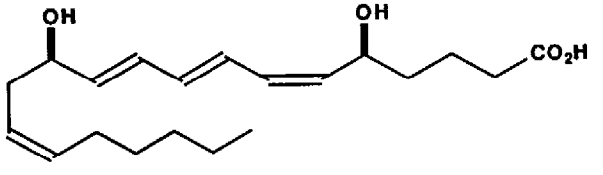
Isoxazoles are familiar and versatile synthetic intermediates,[1] easily made by 1,3-dipolar cycloadditions and easily cleaved to a variety of open chain ketones, enones, and enaminones.[2] 3,5-Dialkyl isoxazoles are also interesting in their own right as they have N-O or O-N functionality inserted into a locally rigid unbranched carbon chain. This curious feature is clearly exhibited by the two isomeric alkenyl isoxazoles (1) and (2): structures which have a similar two-dimensional shape to the leukotrienes,[3] e.g. (3). We report that our phosphine oxide variant[4] of the Horner-Wittig reaction may be used to make either isomer (1) or (2) regiospecifically. The isoxazole ring may either be part of the phosphine oxide reagent (5) or (10), which automatically provides the regiospecificity, or may be added as a 3-acyl isoxazole, which is easily prepared regiospecifically,[2] or as a 5-acyl isoxazole. 1,3-Dipolar cycloadditions to propiolates give mixtures of 4- and 5-acyl isoxazoles[2] but cycloaddition to propargyl alcohols is highly regioselective: oxidation then gives pure 5-acyl isoxazoles. Tsuge has reported some related phosphonates, and related leukotriene analogues have been made.[5]



(1)

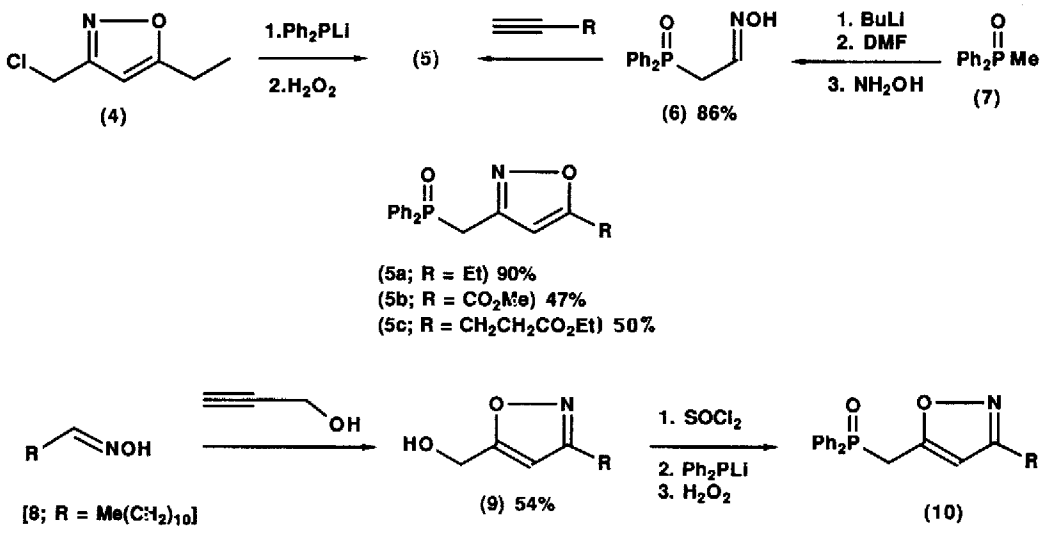


(2)

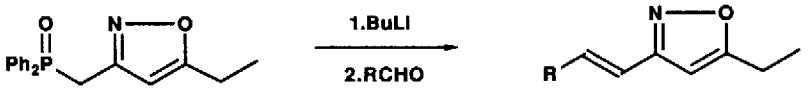


(3) LTB_4

Scheme 1

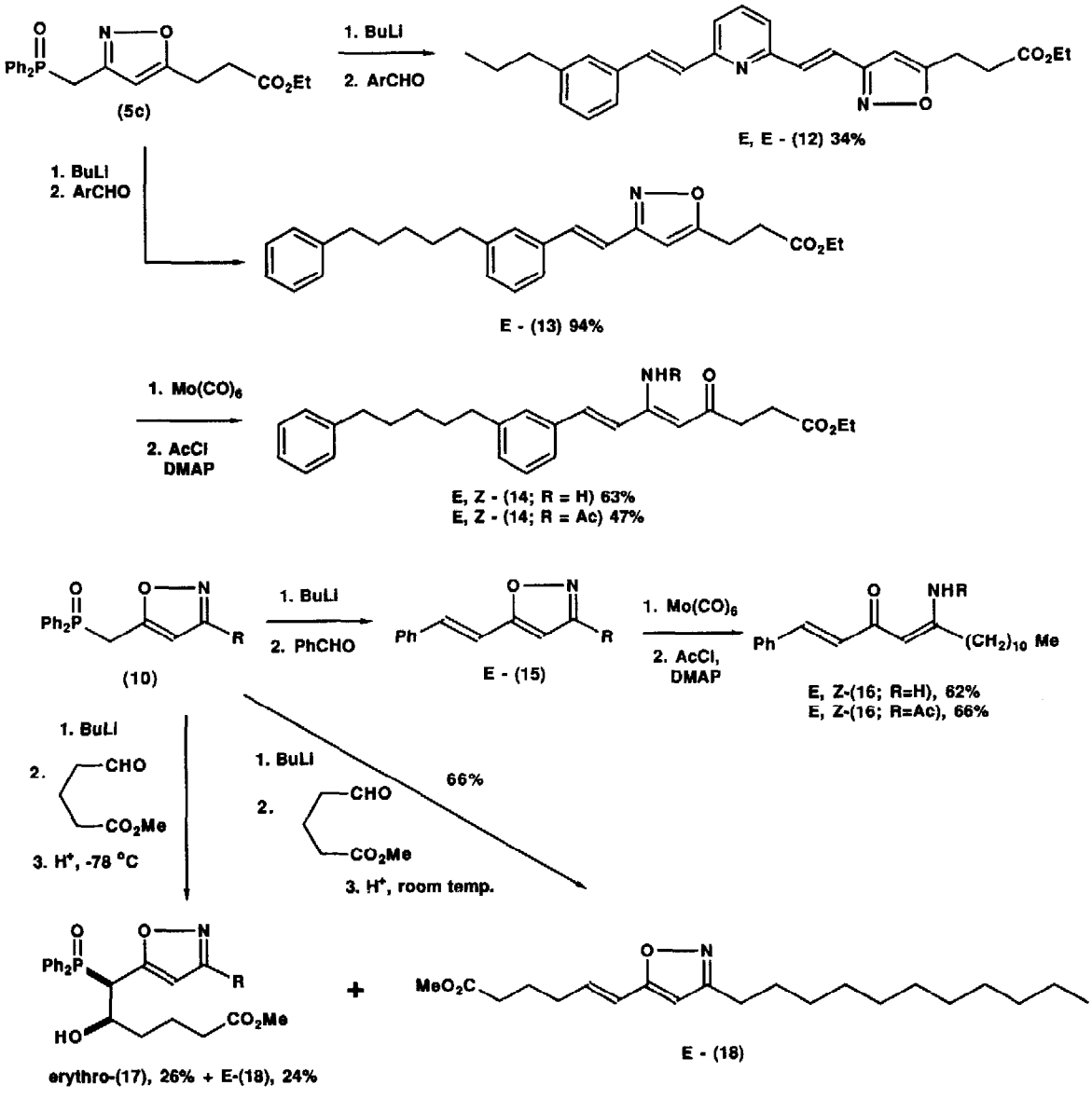


Alkylation at phosphorus [with the halide[6] (**4**)] or 1,3-dipolar cycloaddition of a nitrile oxide (already containing the Ph_2PO group) gives one of the phosphine oxide isomers (**5**): the other (**10**) requires both reactions (scheme 1). Anions from either series (Scheme 2) can be made in the usual way[4] with BuLi or LDA and give β-hydroxyalkylphosphine oxides (**17**) if the reaction is quenched at low temperature. Allowing the reaction to warm to room temperature gives the E-alkenyl isoxazoles (**11**), (**12**), (**13**), (**15**), and (**18**) directly, presumably by equlibration of the intermediate.[7] With aromatic aldehydes, the β-hydroxyalkylphosphine oxides cannot be isolated, E-alkenes being produced in good yield. Treatment of the adduct erythro-(**17**) with NaH in DMF gives the E-alkene (**18**) and starting material (**10**), emphasising that the E-alkenes arise by reversible addition.[4,7]



The alternative approach, addition of an acyl isoxazole to a phosphine oxide (Scheme 3), is not very practical if an aldehyde is used. The formation of (**19**) is not stereoselective (erythro:threo 3:2), separation can be achieved only by h.p.l.c., and elimination of $Ph_2PO_2^-$ from erythro-(**19**) gives a mixture of E and Z-(**20**). However, threo-(**19**) eliminates stereospecifically to give E-(**20**). The all alkyl systems can easily be prepared by acylation and reduction.[8] Either regioisomer (**21**) or (**24**) gives the appropriate ketone (**22**) or

Scheme 2

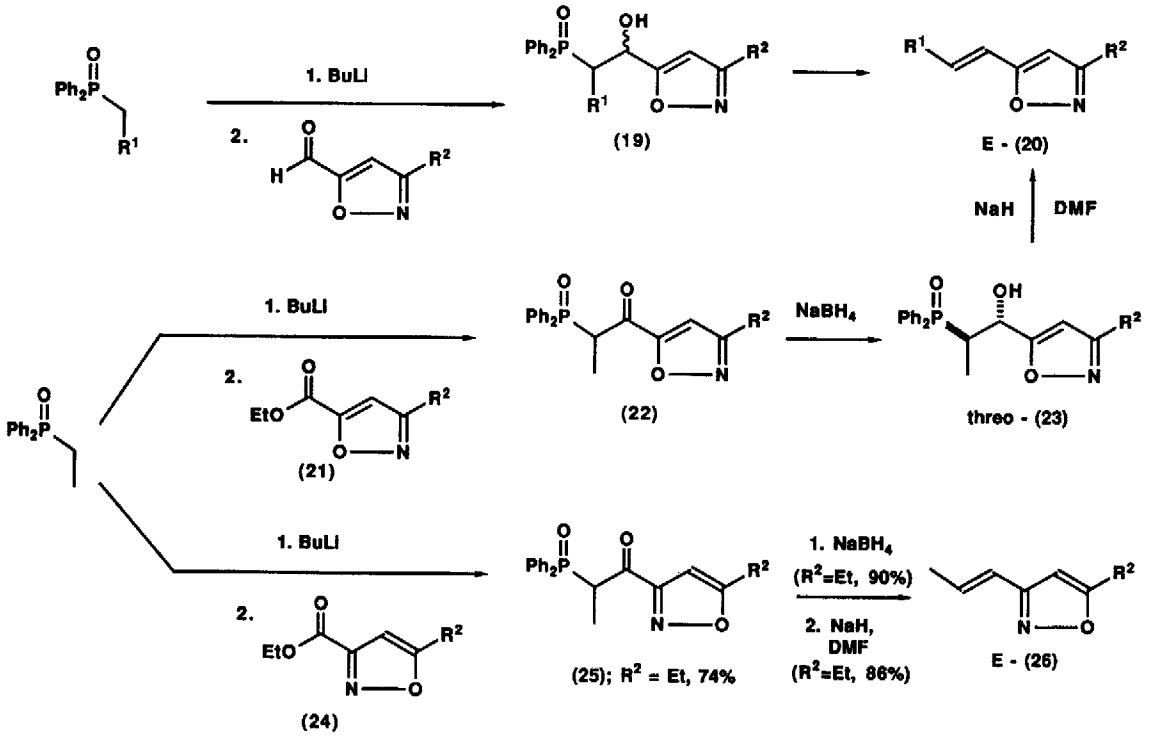


(25), reduction is threo-selective and elimination of $Ph_2PO_2^-$ is stereospecific, giving E-(20) or E-(26) alone. This is an efficient method of preparing 3-alkenyl isoxazoles (26) as the 3-acyl isoxazoles (24) are easily prepared regioselectively. In most cases, however, simple addition of the necessary aldehyde to the lithium derivative of (10) or (5) gives the E-alkene directly in reasonable yield on warming to room temperature.

The unsaturated isoxazole products (11), (12), (13), (15), (18), (20), and (26) are rather sensitive to many of the reagents used to cleave the

isoxazole ring.[2] However, $Mo(CO)_6$ efficiently cleaves[9] the N-O bond to give the enaminones (**14**) and (**16**) in good yield.

Scheme 3



References

1. P.G. Baraldi, A. Barco, S. Benetti, G.P. Pollini, and D. Simoni, Synthesis, 1987, 857.
2. P. Caramella and P. Grünanger in '1,3-dipolar cycloaddition chemistry', ed. A. Padwa, Wiley, New York, 1984, vol. 1, p 291; S.A. Lang and Y. Lin, Comprehensive Heterocyclic Chemistry, eds A.R. Katritzky and C.W. Rees, 1984, vol. 6, p 1; A.P. Kozikowski, Ibid., vol. 1, p 453.
3. R.H. Green and P.F. Lambeth, Tetrahedron, 1983, **39**, 1687; B. Samuelsson, Science, 1983, **220**, 568; Angew. Chem., Int. Ed. Engl., 1983, **22**, 805.
4. A.D. Buss and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1985, 2307; D. Cavalla, W.B. Cruse, and S. Warren, Ibid., 1987, 1883; A.D. Buss, N. Greeves, R. Mason, and S. Warren, Ibid., 1987, 2569.
5. O. Tsuge, S. Kanemasa, and H. Suga, Chem. Lett., 1987, 323; J. Morris and D.G. Wishka, Tetrahedron Lett., 1988, **29**, 143.
6. B.P. Giovanni, M. Fabio, P.G. Piero, S. Daniele, B. Achille, and B. Simonetta, J. Chem. Soc., Perkin Trans. 1, 1982, 2983.
7. A.D. Buss, S. Warren, J.S. Leake, and G.H. Whitham, J. Chem. Soc., Perkin Trans. 1, 1983, 2215.
8. A.D. Buss, R. Mason, and S. Warren, Tetrahedron Lett., 1983, **24**, 5293.
9. M. Nitta and T. Kobayashi, J. Chem. Soc., Chem. Commun., 1982, 877.

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