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HIGHLY STEREOSELECTIVE RADICAL ADDITION TO A TRISUBSTITUTED ALKENE BY LOW TEMPERATURE PHOTOLYSIS OF THIOHYDROXAMIC ESTERS

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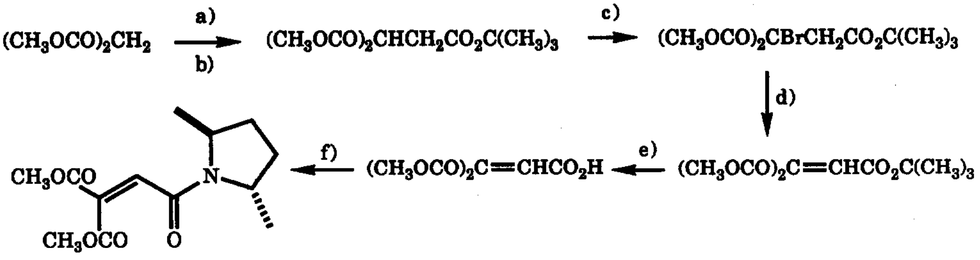
Abstract: *Low temperature carbon radical addition to α,β-unsaturated amides of trans-2,5-dimethylpyrrolidine was achieved in high yield with high diastereoselectivity by photolysis of Barton esters. Use of an olefin substituted with three electron withdrawing groups provides synthetic versatility and regiospecificity.*

We have recently reported the results of a study in which we achieved unprecedented diastereoselectivity in the intermolecular addition of carbon radicals to conjugated amides of *trans*-2,5-dimethylpyrrolidine.[1] In the initial work, radical addition was performed by the "tin method", or by the "mercury method",[2] and a large temperature dependence was observed for the diastereoselectivity over the experimentally allowed temperature range of 0°C to 110°C. Since enhanced selectivity is anticipated at low temperature, a method for radical addition at low temperatures is of considerable practical importance. Other problems associated with the earlier study were the moderate yields of addition products obtained and a lack of regioselectivity in the additions to the unsymmetrical alkene examined. In this work we have studied a synthetically versatile olefin which limits radical addition to the amide substituted end of the double bond, and we have utilized the "Barton method" for low temperature radical addition. Regioselectivity, diastereoselectivity and product yield are all greatly improved by these modifications of substrate and method.

Alkenes substituted with three electron withdrawing groups undergo radical addition exclusively at their monosubstituted terminus,[3] and the alkene 1 thus became an attractive target for study. Synthesis of 1 is shown in Scheme 1. Dimethyl malonate was alkylated with t-butyl bromoacetate, followed by bromination and dehydrobromination, producing the olefinic triester. The t-butyl group was selectively removed using trifluoroacetic acid in dichloromethane,[4] followed by formation of the amide *via* the isobutyl carbonate mixed anhydride. This produced olefin 1 as a colorless solid, mp 80-81°C.[5] This simple synthesis is adaptable to a wide variety of malonate-like starting materials.

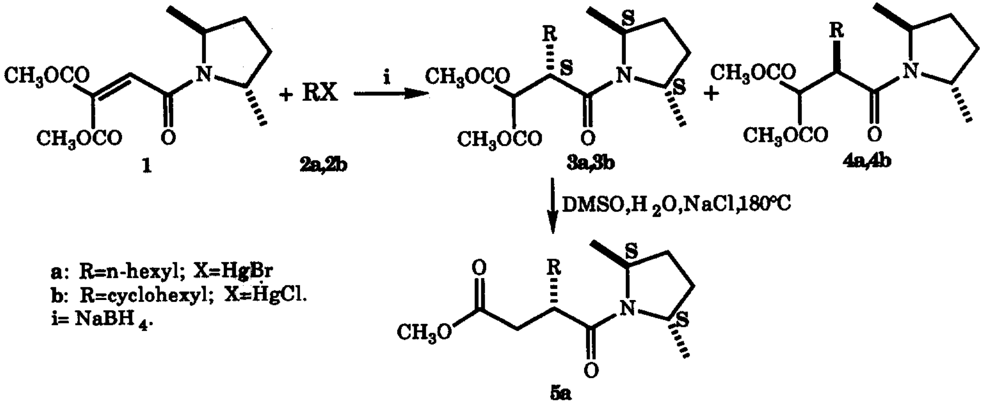
SCHEME 1



a) NaH, THF; b) t-butyl bromoacetate; c) NBS, $(PhCO_2)_2$, CCl_4; d) Et_3N, Et_2O; e) CF_3CO_2H, CH_2Cl_2; f) iBuOCOCl, N-methylmorpholine, 2(S),5(S)-dimethylpyrrolidine.

Addition of n-hexyl radical to **1** by the mercury method produced adducts **3a** and **4a** (Scheme 2) in a ratio of 16:1. This electron deficient olefin is especially susceptible to reduction, and in the case of the primary alkyl radical, reduced olefin was the major isolated product, accounting for 50% of starting material. The stereochemical configuration of the major adduct, **3a**, was assigned by performing a decarboxylation in refluxing wet DMSO in the presence of catalytic NaCl,[6] directly forming **5a**. This product was identical in all respects to an authentic sample produced previously.[1] Cyclohexyl radical addition to **1** by the mercury method produced adducts **3b** and **4b** in a ratio of 40:1. The major adduct was obtained in 49% yield as a crystalline solid. The stereochemical assignment of the all (S) configuration to **3b** was provided by X-ray crystallography of the racemic compound.[7] In the solid state, the cyclohexyl group is disordered over two orientations as shown in Figure 1.

SCHEME 2



a: R=n-hexyl; X=HgBr
b: R=cyclohexyl; X=HgCl.
i= $NaBH_4$.

Low temperature radical generation has been accomplished by photolysis of mixed thiohydroxamic anhydrides, or Barton esters, such as **6**.[8] We found that radical addition could be performed by combining the olefin with 1.5 molar equivalents each of the Barton ester and tributyltin hydride in dichloromethane (25 mM in olefin).

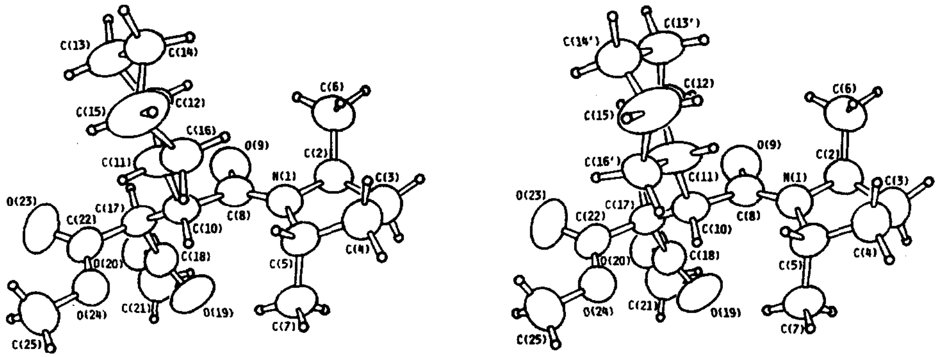
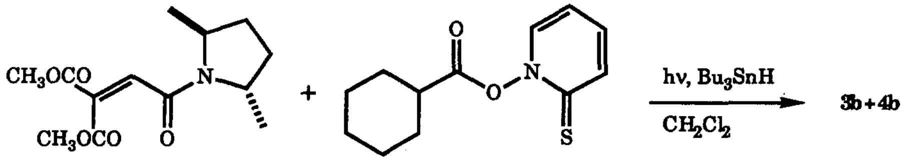


Figure 1. Structure of one enantiomer of **3b** illustrating the two orientations adopted by the disordered cyclohexyl group in the solid state.

The trisubstituted olefin **1** proved to be a very efficient alkyl radical scavenger and underwent nearly complete conversion in the presence of tributyltin hydride as a hydrogen atom source. The light source was a 100W tungsten filament lamp held at a distance of 30 cm from the reaction vessel. Irradiation was continued until the bright yellow color of the Barton ester disappeared (4 to 8 hours). At 25°C this procedure produced **3b** and **4b** in a ratio of 45:1, with a 67% yield of **3b**. The reaction was then performed at -78°C using a custom-made pyrex Dewar vessel. Radical addition by this method produced **3b** and **4b** in a ratio of >125:1, providing **3b** in yields in excess of 90%. Performing the reaction at -78°C appeared to eliminate competing reduction of the olefin.

SCHEME 3



1

6

Method	Products	Ratio	
0°C, Hg method	**3a : 4a**	16:1	
0°C, Hg method	**3b : 4b**	40:1	yield **3b** = 49%
25°C, Barton method	**3b : 4b**	45:1	yield **3b** = 67%
-78°C, Barton method	**3b : 4b**,	>125:1	yield **3b** = >90%

The approach presented here represents a significant improvement in the methodology of intermolecular radical additions. Excellent stereoselectivity can be obtained in conjunction with high yields of addition products. The advantage of the C_2 symmetric chiral auxiliaries, like *trans*-2,5-dimethylpyrrolidine, has been thoroughly documented in other asymmetric synthetic applications,[9] and we believe that this report indicates the utility of these auxiliaries in the field of free-radical synthetic chemistry.

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References

1. Porter, N. A.; Scott, D. M.; Lacher, B. L.; Giese, B.; Zeitz, H. G.; Lindner, H. J. *J. Am. Chem. Soc.*;1989; *111*: 8311.
2. For a review of these methods see Giese, B. *Angew. Chem, Int. Ed. Engl.*;1985; *24*: 553.
3. Hall, H. K., Daly, C. D. *Macromolecules*; 1975; *8 (1)*:22.
4. Kelly, T. R. *Tet. Lett.*; 1973; *6*:437.
5. All new compounds cited in this article gave satisfactory elemental analyses and spectral data.
6. Krapcho, A. P., Lovey, A. J. *Tet. Lett.*; 1973; *12*: 957.
7. Crystal data (±)-**3b**, $C_{19}H_{31}NO_5$, monoclinic, space group $\underline{P}2_1/\underline{c}$, $\underline{a} = 13.131(2)$ Å, $\underline{b} = 6.336(1)$ Å, $\underline{c} = 23.962(2)$ Å, $\beta = 94.48(1)°$ (from 25 orientation reflections, $41° < \theta < 48°$), $\underline{V} = 1987.5\ (9)$ Å^3, $\underline{Z} = 4$, $\underline{D}_c = 1.181$ g cm^{-3}, μ (Cu-$\underline{K}\alpha$ radiation, $\lambda = 1.5418$ Å) = 6.5 cm^{-1}; crystal size: 0.22 x 0.22 x 0.40 mm. Intensity data ($+h$, $+k$, $\pm\ell$; 4068 refls.; $\theta_{max.} = 75°$) were recorded on an Enraf-Nonius CAD-4 diffractometer [Cu-$\underline{K}\alpha$ radiation, graphite monochromator; ω-2θ scans; scanwidth $(0.90 + 0.14\tan\theta)°$]. Initial coordinates for all non-hydrogen atoms, save those of methylene carbon atoms of the cyclohexyl moiety, were obtained from an $\underline{E}$-map (MULTAN11/82). Several rounds of adjustment of parameters for these atoms were followed by evaluation of a difference Fourier synthesis from which approximate coordinates were derived for the disordered cyclohexyl carbon atoms. Full-matrix least-squares refinement (Enraf-Nonius SDP) of atomic positional and thermal parameters (anisotropic C, N, O; isotropic ordered H; fixed cyclohexyl H) converged at $\underline{R} = 0.050$ ($\underline{R}_w = 0.078$) over 2630 reflections with $\underline{I} > 3.0\sigma(\underline{I})$. Atomic parameters, bond lengths, and angles have been deposited at the Cambridge Crystallographic Data Centre.
8. Barton, D. H. R., Bridon, D., Fernandez-Picot, I., Zard, S. Z. *Tetrahedron*; 1987; *43 (12)*: 2733.
9. (a) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.*; 1977; *42*:1663; (b) Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; p 2; (c) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; p 111; (c) Lutomski, K. A.; Meyers, A. I. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; p 213.

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