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EFFICIENT SYNTHESIS AND INTRAMOLECULAR CYCLOPROPANATION OF UNSATURATED DIAZOACETIC ESTERS

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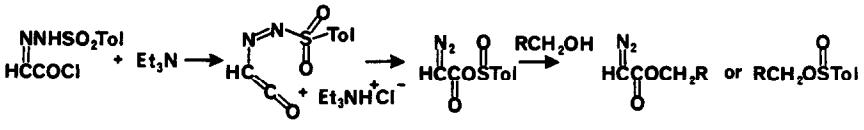
Summary: New and efficient procedures are described for the conversion of homoallylic alcohols to esters of diazoacetic acid and for the further intramolecular cyclopropanation of those esters.

As part of a program directed towards the synthesis of the antheridiogen of Anemia phyllitidis, A_{An},[1] we required an efficient means of transforming alcohol 1 via its diazoester 2, to cyclopropyllactone 3. The method of House and Blankley which involves the reaction of glyoxylic acid chloride p-toluenesulfonylhydrazone and triethylamine with an alcohol, has been widely used for the preparation of diazoacetic esters.[2] Application of this procedure to a model substance, the alcohol 4[3] afforded at best a 2.5 : 1 mixture of the desired diazoacetate 5 and the p-toluenesulfinate ester 6 in a total yield of 65%.[4] An examination of the literature[5] as well as our experience with the reaction suggest that this side reaction may be general and that achievable yields are in the range 40-55% (as in the preparation of cretyl diazoacetate[6]). The formation of p-toluenesulfinate ester can be rationalized as the result of a process such as the following:



Indeed, infrared analysis demonstrated that triethylamine promotes the conversion of glyoxylic acid chloride tosylhydrazone to a diazo compound within a few minutes at room temperature in methylene chloride. In order to circumvent this base induced side reaction the use of a weaker base, N,N-dimethylaniline, in the reaction was examined. It was found that dimethylaniline promotes clean reaction between glyoxylic acid chloride tosylhydrazone and alcohols to form the corresponding esters (detected by thin layer chromatography-tlc) which upon further reaction (in situ) with triethylamine are converted to diazoacetic esters. Thus the alcohol 4 was converted to diazo ester 5 in 70% isolated yield with no detectable sulfinate by-product 6 by tlc analysis. Use of this modified procedure has provided the pure diazoacetate of 3-vinylcyclohex-2-enol, 7[7] (76%), and (1R, 2S, 5R)-2-(dimethylbenzyl)-5-methyl-cyclohexanol, 8,[8] (77%).

The method is illustrated in the preparation of diazoester 2.

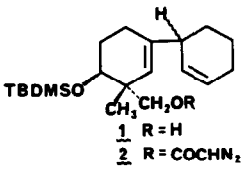
Thermal decomposition of diazoester 2 using a stirred suspension of copper powder in toluene at reflux afforded cyclopropyllactone 3 in 57% yield. However, it was found that the yield of 3 dropped substantially on scale-up evidently as a consequence of the hetereogeneous reaction conditions. Use of bis-(N-t-butylsalicylaldiminato) copper (II), a soluble catalyst,[10] coupled with slow introduction of diazoester into the reaction mixture afforded an excellent yield of cyclopropyllactone 3 regardless of scale. This procedure also provided lactone 10 from diazoester 9 in 92% yield.

Diazoester 2: Glyoxylic acid chloride p-toluenesulfonylhydrazone[6] (15.2 g, 58.3 mmol) was added to an ice-cooled solution of dry alcohol 1 (a 1 : 1 mixture of epimers, as shown, 10.51 g, 31.2 mmol) in 180 mL of dry methylene chloride under an argon atmosphere. Dimethylaniline (7.25 mL, 57.2 mmol) was added and the dark green solution was stirred for 15 min prior to injection of triethylamine (22 mL, 160 mmol). The resulting dark orange suspension was stirred 10 min at 0° then for 15 min at room temperature before water (125 mL) was introduced and the mixture was concentrated in vacuo. Saturated aqueous citric acid (250 mL) and 10% ethyl acetate-hexanes (250 mL) were added and the layers were separated. The organic layer was washed with 250 mL citric acid solution and the combined aqueous layers were extracted with 100 mL 10% ethyl acetate-hexanes. This 100 mL extract was washed with an equal volume of citric acid solution and the combined organic layers were dried over sodium sulfate. Concentration and flash chromatography[9] (5% ethyl acetate-hexanes) provided 2 as a yellow syrup (11.44 g, 90.5%); ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.75 (m, 1H), 5.46 (m, 1H), 5.07 and 5.09 (s, 1H), 4.69 and 4.71 (s, 1H), 4.02 and 4.05 (d, 1H, J=10.5 Hz), 3.91 (d, 1H, J=10.5 Hz), 3.78 (m, 1H), 2.62 (bs, 1H), 1.9-2.15 (m, 4H), 1.35-1.8 (m, 6H), 0.91 (s, 3H), 0.89 (s, 9H), 0.03 and 0.06 (s, 6H); IR (neat film, cm.$^{-1}$): 3123, 2112, 1701, 1253, 1105; MS: 376 ($M^+ - N_2$), 347 (M^+-t-Bu).

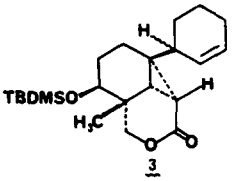
Cyclopropyllactone 3: A solution of diazoester 2 (from the experiment described above, 11.44 g, 28.3 mmol, 1 equiv) in 607 mL toluene was added dropwise from a constant rate addition funnel to a mechanically stirred, refluxing solution of bis-(N-t-butylsalicyladiminato)copper (II) catalyst[11] (0.63 g, 1.5 mmol, 0.05 equiv) in 625 mL toluene at an initial rate of 60 mL/h and after 2 h at a rate of 42 mL/h (total addition time 14 h). The solution was held at reflux 20 min after completion of addition, cooled, concentrated and purified by flash chromatography[9] (2% triethylamine - 10% ethyl acetate-hexanes). The yield of purified lactone 3 was 8.93 g, 84%; ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.6-5.8 (m, 2H), 4.09 and 4.10 (d, 1H, J=11.5 Hz), 3.77 (d, 1H, J=11.5 Hz), 3.50 (bs, 1H), 1.93-2.0 (bs, 3H), 1.5-1.9 (m, 8H), 1.39 and 1.45 (d, 1H, J=8 Hz), 1.18 (d, 1H, J=8 Hz), 1.14 and 1.16 (s, 3H), 0.92 and 0.93 (s, 9H), 0.06 and 0.07 (s, 6H): IR (CCl_4, cm.$^{-1}$): 1741; MS: 319 (M^+-t-Bu).

Cyclopropyllactone 10: A toluene solution of diazoester 9 (10.0 mL, 8.94 mg/mL, 0.465 mmol) was added dropwise via syringe drive over 16.5 h to a refluxing solution of bis-(N-t-butylsalicylaldiminato) copper (II) (10.4 mg, 0.025 mmol, 5.4 mole pct) in toluene (10.0 mL). After completion of the addition, the solution was held at reflux 30 min, cooled, concentrated in vacuo and the residue was purified by bulb to bulb distillation (110-120°, 1.2 mm) giving 72.1 mg yellow liquid product (contaminated with about 1 mole pct t-butylsalicylaldimine, corrected yield 92%). The contaminating salicylaldimine can be removed from the lactone by washing an ethereal solution with a small amount of cold dilute hydrochloric acid to provide pure 10 as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.46 (dd, 1H, J=10, 17 Hz), 5.04 (d, 1H, J=17 Hz), 5.03 (d, 1H, J=10 Hz), 4.95 (m, 1H), 2.33 (t, 1H, J=6 Hz), 2.1-2.2 (m, 2H), 1.45-2.0 (m, 5H); IR (neat film, cm.$^{-1}$): 1758, 1636; MS: 164 (M^+).

The improved methodology reported herein adds considerably to the utility of the diazoacetate ⟶ cyclopropyllactone conversion in synthesis.[12]



1 R=H
2 R=COCHN$_2$



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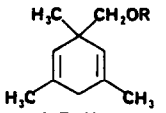
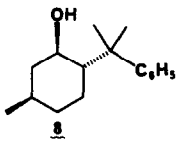


4 R=H
5 R=COCHN$_2$
6 R=p-TolSO-



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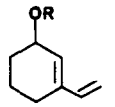
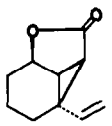


7 R=H
9 R=COCHN$_2$



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References and Notes

1. K. Nakanishi, M. Endo, U. Näf, and L. F. Johnson, J. Am. Chem. Soc., 93, 5579 (1971).

2. H. O. House, C. J. Blankley, J. Org. Chem., 33, 53 (1968).

3. Prepared in 70% overall yield by lithium aluminum hydride reduction of the product from reductive Birch alkylation of 3,5-dimethylbenzoic acid; see H. Van Bekkum, C. B. Van Den Bosch, G. Van Minnenpathuis, J. C. DeMos, and A. M. Van Wijk, Rec. Trav. Chim., 90, 137 (1971).

4. For 5: ^{1}H NMR (80 MHz, $CDCl_3$): δ 5.12 (bs, 1H), 4.62 (s, 1H), 3.82 (s, 2H), 2.35 (bs, 2H), 1.70 (s, 6H), 1.00 (s, 3H); IR (neat film, cm.$^{-1}$): 3112, 2112, 1701. For 6: ^{1}H NMR (80 MHz, $CDCl_3$): δ 7.60 (d, 2H, J=8 Hz), 7.31 (d, 2H, J=8 Hz), 5.15 (m, 2H), 3.74 (d, 1H, J=9 Hz), 3.21 (d, 1H, J=9 Hz), 2.43 (bs, 5H), 1.72 (s, 6H), 1.00 (s, 3H); IR (neat film, cm.$^{-1}$): 1139.

5. Recently cholesteryl p-toluenesulfinate has been tentatively identified as a by-product in the preparation of cholesteryl diazoacetate; see S. A. Keilbaugh and E. R. Thornton, J. Am. Chem. Soc., 105, 3283 (1983).

6. C. J. Blankley, F. J. Sauter and H. O. House, Organic Syntheses, Coll. Vol. V, p. 258; John Wiley, New York (1973).

7. Prepared in 75% overall yield from 3-ethoxycyclohex-2-enone by the following sequence: vinylmagnesium bromide, H^+, $NaBH_4/CeCl_3$ (see J.-L. Luche, J. Am. Chem. Soc., 100, 2226 (1978)).

8. E. J. Corey and H. E. Ensley, J. Am. Chem. Soc., 97, 6908 (1975). This experiment was performed by Dr. Chi-nung Hsiao.

9. W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2923 (1978).

10. H. Nozaki, H. Takaya, S. Moriuti, and R. Noyori, Tetrahedron, 24, 3655 (1968) and H. Hirai and M. Matsui, Agr. Biol. Chem., 40, 169 (1976).

11. Prepared in quantitative yield by the method of R. G. Charles (J. Org. Chem., 22, 677 (1957)). Recrystallization from methanol afforded large, black prisms mp 184-185° (lit mp 185-186°): calcd for $C_{22}H_{28}CuN_2O_2$: C, 63.52; H, 6.78; N, 6.73; found: C, 63.47; H, 6.64; N, 6.79. (See L. Sacconi and M. Ciampolini, J. Chem. Soc., 276 (1964)).

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