3.89 (q, 2), 7.14-8.58 (m, 8). Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 51.5; H, 5.1. Found: C, 51.6; H, 5.0.

5-(2-Propen-1-yl)-5-(phenylsulfonyl)-6-oxo-5,6,7,8-tetrahydroquinoline (38) from 34 and allyl bromide (85%): mp 96-97 °C (hexane/chloroform); IR ($CHCl_3$) 1720 cm^{-1}; NMR δ 2.25-3.40 (m, 6), 4.82-5.21 (m, 3), 7.20-8.60 (m, 8). Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 69.5; H, 5.2. Found: C, 69.5; H, 5.1.

5-Methyl-6-oxo-5,6,7,8-tetrahydroquinoline (39) and 5-[(ethoxycarbonyl)methyl]-6-oxotetrahydroquinoline (40) were obtained from **36** and **37**, respectively, as described for **35**, by treatment with Raney nickel. Compound **39** was obtained as an oil, unstable in air: bp 78 °C (0.3 mm); 98%; IR 1718 cm^{-1}; NMR δ 1.49 (d, J = 7 Hz, 3), 2.55-2.98 (m, 3), 3.22-3.59 (m, 2), 7.20 (dd, J = 3 Hz, 4 Hz, 1), 7.51 (d, J = 4 Hz, 1), 8.44 (J = 3 Hz, 1); mass spectrum, m/e 161 (M^+), 132.

Compound **40** was obtained as an oil: bp 102 °C (0.2 mm); 71%; IR ($CHCl_3$) 1720 cm^{-1}; NMR δ 1.22 (t, 3), 2.60-2.83 (m, 2), 3.04 (d, J = 6 Hz, 2), 3.27-3.44 (m, 2), 3.85-4.26 (m, 3), 7.20 (dd, J = 4, 7 Hz, 1), 7.46 (d, J = 7 Hz, 1), 8.44 (d, J = 4 Hz, 1); mass spectrum, m/e 233 (M^+), 187.

5-Methyl-6-hydroxyquinoline (41) and 5-[(Ethoxycarbonyl)methyl]-6-hydroxyquinoline (42). To a solution of 33 mg (0.3 mmol) of t-BuOK in 1.5 mL of dry t-BuOH was added under nitrogen 0.1 mmol of **36** or **37**, respectively, dissolved in 3 mL of dry THF, and the mixture was stirred at room temperature for 1 h, poured into ice and brine, and extracted with chloroform (3×). The usual isolation gave **41** in 88% yield: mp 173-174 °C (chloroform/hexane); IR (KBr) 1575, 1500, 1405, 1330, 1260 cm^{-1}; λ_{max} 288 nm (ϵ 2500), 335 (3600); NMR δ 2.54 (s, 3), 7.26-8.24 (m, 5); mass spectrum, m/e 159 (M^+),]30. Anal. Calcd for $C_{10}H_9NO$: C, 74.5; H, 5.7. Found: C, 74.6; H, 5.8.

Compound **42** was isolated in 84% yield: mp 181 °C (chloroform/hexane); IR (KBr) 1730, 1580, 1510, 1330, 1270, 1180 cm^{-1}; UV λ_{max} 285 nm (ϵ 3000), 335 (4300); NMR δ 1.25 (t, 3), 4.08 (s, 2), 4.18 (q, 2), 7.18-8.76 (m, 5); mass spectrum, m/e 231 (M^+), 185, 157, 130. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.6. Found: C, 67.8; H, 5.6.

7-Oxo-8-(phenylsulfonyl)-5,6,7,8-tetrahydroquinoline (44). To a stirred mixture of t-BuOK (0.15 g) in dry THF (10 mL) under argon was added 0.15 g (0.45 mmol) of ester **43** dissolved in 15 mL of THF. After being stirred for 1 h at room temperature, the mixture was poured into water, and the aqueous solution was acidified with dilute aqueous HCl and then brought to pH 8 with aqueous Na_2CO_3. Extraction with chloroform (3×) and isolation in the usual manner gave 92 mg (71% yield) of **44** which crystallized directly on being washed with pentane/20% ether: mp 236-238 °C dec; UV λ_{max} 295 nm (ϵ 10500), 359 (16000); IR (KBr) 1560-1580 cm^{-1} (vs); NMR δ 2.31-2.47 (m, 2), 2.68-3.09 (m, 2), 6.64 (t, 1), 7.21-8.09 (m, 7); mass spectrum, m/e 287 (M^+), 223, 222, 146, 118. Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.7; H, 4.5. Found: C, 62.6; H. 4.6.

7-Hydroxy-8-methylquinoline (46). Keto sulfone **44** (60 mg, 0.21 mmol) was treated with MeI as described for the preparation of **36** by adding 600 mol % of MeI in several portions during 1 h at which time all the **44** had been converted to the less polar **45**. The residue from isolation was dissolved in THF (4 mL) and added to a solution of t-BuOK (50 mg) in t-BuOH (2 mL). After being stirred for 1 h at room temperature, the mixture was poured into ice-water and extracted with chloroform, and the residue was purified on a silica column (eluting with ether) to give 15 mg of **46** (46% from **44**): mp 189 °C; IR (KBr) 1610, 1580, 1480, 1320, 1270 cm^{-1}; UV λ_{max} 270 nm (ϵ 2500), 333 (4500); NMR δ 2.69 (s, 3), 7.11-7.30 (m, 2), 7.57 (d, J = Hz, 1), 8.03 (dd, J = 9, 2 Hz, 1), 8.87 (dd, J = 4, 2 Hz, 1); mass spectrum, m/e 159 (M^+), 131, 130. Anal. Calcd for $C_{10}H_9NO$: C, 74.5; H, 5.7. Found: C, 74.8; H, 5.7.

Ketone **45** was isolated from a separate experiment by omitting the *tert*-butoxide treatment and concluding with chromatography and ether/2% methanol elution: mp 135 °C (hexane/chloroform); IR 1712 cm^{-1}; UV λ_{max} 266 nm (ϵ 6500); NMR δ 1.86 (s, 3), 2.48-3.90 (m, 4), 7.26-8.43 (m, 8); mass spectrum, m/e 301 (M^+), 160. Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.8; H, 5.0. Found: C, 63.9; H, 5.1.

Registry No. **1**, 583-61-9; **2**, 76915-52-1; **3**, 76915-53-2; **4**, 76915-54-3; **5**, 1721-26-2; **6**, 56826-61-0; **7**, 73843-36-4; **8**, 76915-55-4; **9** (isomer 1), 76915-56-5; **9** (isomer 2), 76915-57-6; **10** (isomer 1), 76915-58-7; **10** (isomer 2), 76915-96-3; **11** (isomer 1), 76915-59-8; **11** (isomer 2), 76915-60-1; **12** (isomer 1), 76915-61-2; **12** (isomer 2), 76915-62-3; **13**, 76915-63-4; **14**, 76915-64-5; **15**, 76915-65-6; **16**, 76915-66-7; **17** (isomer 1), 76915-67-8; **17** (isomer 2), 76915-68-9; **18**, 76915-69-0; **19**, 76915-70-3; **20**, 76915-71-4; **21**, 76915-72-5; **22**, 76915-73-6; **23**, 76915-74-7; **24**, 76915-75-8; **25**, 76915-76-9; **26**, 76915-77-0; **27**, 76915-78-1; **28**, 76915-79-2; **29**, 76915-80-5; **30**, 76915-81-6; **31**, 7605-25-6; **32**, 76915-82-7; **33**, 76915-83-8; **34**, 76915-84-9; **35**, 27463-91-8; **36**, 76915-85-0; **37**, 76915-86-1; **38**, 76915-87-2; **39**, 76915-88-3; **40**, 76915-89-4; **41**, 76915-90-7; **42**, 76915-91-8; **43**, 76915-92-9; **44**, 76915-93-0; **45**, 76915-94-1; **46**, 76915-95-2; azobis(isobutyronitrile), 78-67-1; isobutyraldehyde, 78-84-2; 2-butanone, 78-93-3; ethyl bromoacetate, 105-36-2; 1-buten-3-one, 78-94-4; allyl bromide, 106-95-6; propargyl bromide, 106-96-7.

Bis Heteroannulation. 2. Oxazole Alcohols from the Interaction of Lithiomethyl Isocyanide with Lactones. A Novel Synthesis of Evodone

Peter A. Jacobi,* Donald G. Walker, and Imad M. A. Odeh

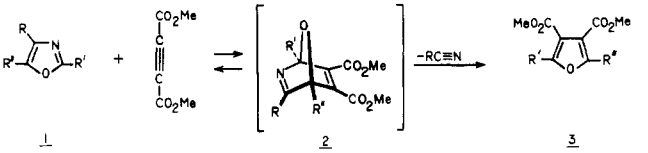
Hall-Atwater Laboratories, Wesleyan University, Middletown, Connecticut 06457

Received January 22, 1981

Oxazole alcohols may be readily obtained through the interaction of lithiomethyl isocyanide with lactones. Acetylenic oxazoles of proper design have been shown to undergo a facile intramolecular Diels-Alder reaction, leading directly to fused-ring furan derivatives of the type found in the furanosesquiterpenes ("bis heteroannulation"). A novel synthesis of evodone is presented.

The extraordinary reactivity of the oxazoles in Diels-Alder reactions has led to their widespread use in natural product synthesis. Reaction with alkenes, for example, leads directly to highly substituted pyridine derivatives,[1] a transformation extensively utilized in the synthesis of pyridoxine derivatives[2] and recently applied in a novel synthesis of the antitumor agent ellipticine.[3] Alternatively, reaction with acetylenic dienophiles provides an

Scheme I

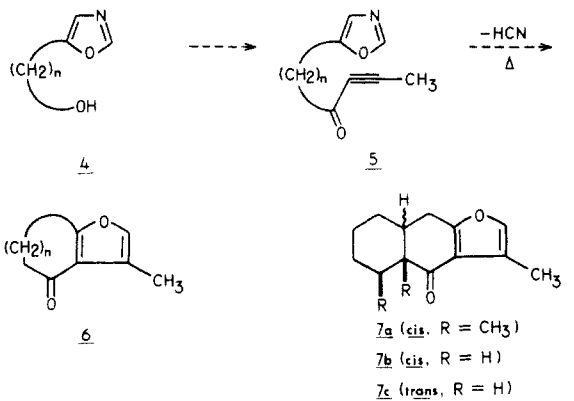


1 2 3

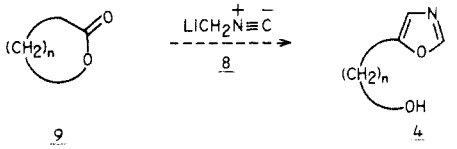
(1) Katritzky, A. R.; Boulton, A. J. Eds. "Advances in Heterocyclic Chemistry"; Academic Press: New York, New York, 1974; Vol. 17.

0022-3263/81/1946-2065$01.25/0

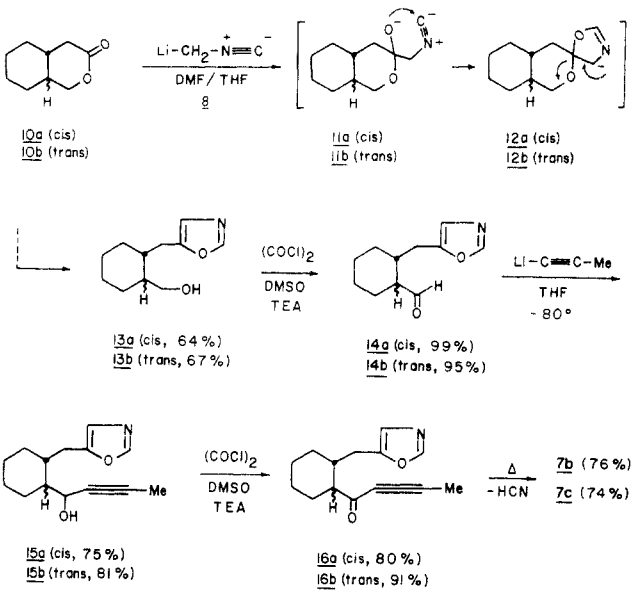
Scheme II



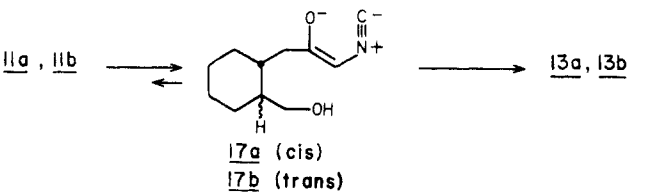
Scheme III



Scheme IV



Scheme V



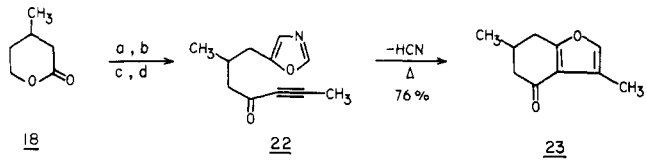
excellent route to highly substituted furans of type **3**.[1,4] (see Scheme I). Although this latter conversion has attracted considerably less attention, it is of interest that such a process, if applied in an intramolecular sense, could provide a facile entry to the synthesis of furanoterpenes (Scheme II). We have suggested the term bis heteroannulation for this type of reaction sequence.[5]

It is interesting to note that the vast majority of the furanoterpenes contain both a β-methyl substituent on the furan ring and an oxygen functionality at a position adjacent to the furan ring junction (cf. ligularone (**7a**), for example). As indicated above, both of these groups could, in principle, be transposed intact from acetylenic ketone precursors such as **5**. These latter materials, in turn, should be easily derivable from oxazole alcohols of type **4**.[6] In this paper we describe a simple procedure for the synthesis of oxazole alcohols **4** and the further transformation of these materials to multicyclic systems having the basic skeleton of the eudesmane and eremophilane classes of furanosesquiterpenes. In addition, we report a novel synthesis of evodone,[7] the simplest member of the naturally occurring furanoterpenes.

From a conceptual standpoint the most attractive route to **4** would involve a Schöllkopf reaction of lithiomethyl isocyanide (**8**, Scheme III) with the corresponding lactone derivative **9**. Such reactions can be routinely carried out with esters, anhydrides, and acid chlorides.[8] Surprisingly, however, we could find only one report describing the attempted reaction of metalated isocyanides with lactone derivatives,[9] and these authors obtained an "intractable mixture" under the standard reaction conditions. We have confirmed these results in our initial attempts to convert lactone **10a** to the oxazole alcohol **13a** (Scheme IV). Thus, reaction of **10a** with **8** (~2.2 equiv) in THF at temperatures ranging from −78 °C to 25 °C gave only trace amounts of the desired oxazole alcohol **13a**. Although yields of up to 22% could be obtained upon prolonged reflux (3–6 days), these reactions were always accompanied by substantial decomposition to polymeric material. Also, in several instances material analyzing for dimeric species (two parts **10a**, one part **8**) could be isolated from the tarry reaction mixtures. These results are in marked contrast to the excellent yields normally obtained with ester derivatives.[3,8] On analysis of this reaction two facts could be established with certainty. First, the conversion of **10a** to **11a** was rapid even at −78 °C, since **11a**, in equilibrium with its open-chain isomer, could be cleanly isolated upon immediate quenching with acetic acid. Second, the desired conversion of **11a** to the oxazole alcohol **13a** was evidently extremely slow and subject to favorable competition from intermolecular pathways. These alternative pathways, however, could be partially eliminated through the addition of ~33% per unit volume of DMF. This solvent had a dramatic accelerating influence on the conversion of **11a** to **13a**, and yields in the range of 30–40% could be obtained after 16 h at ambient temperature. Finally, almost all side reactions were eliminated by working in higher dilution and in the presence of no more than 1.1 equiv of **8**. At an optimal concentration of 0.12 M we were thus able to obtain yields of 60–80%, after crystallization, of oxazole alcohol **13a**. In a similar fashion, lactone **10b** gave ~70% of the corresponding trans-fused oxazole alcohol

(2) Firestone, R. A.; Harris, E. E.; Reuter, W. *Tetrahedron* **1967**, *23*, 943 and references cited therein.
(3) Kozikowski, A. P.; Hasan, N. M. *J. Org. Chem.* **1977**, *42*, 2039.
(4) (a) Grigg, R.; Hayes, R.; Jackson, J. L. *J. Chem. Soc. D* **1969**, 1167. (b) Grigg, R.; Jackson, J. L. *J. Chem. Soc. C* **1970**, 552. (c) Kondrateva, G. Y.; Medvedskaya, L. B.; Ivanova, Z. N. *Chem. Abstr.* **1972**, *76*, 59332. (d) Graf, R. German Offen. 1 935 009, Jan 14, 1971.
(5) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748.
(6) Brandsma, L. "Preparative Acetylenic Chemistry"; Elsevier: New York, 1971.
(7) Birch, A. J.; Rickards, R. W. *Aust. J. Chem.* **1956**, *9*, 241.
(8) (a) Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 333. (b) Hoppe, D. *Ibid.* **1974**, *13*, 789. (c) Schöllkopf, U. *Pure Appl. Chem.* **1979**, *51*, 1347. (d) Walborsky, H. M.; Pereasamy, M. P. *Org. Prep. Proced. Int.* **1979**, *11*, 293. (e) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1980**, *102*, 860. See also ref 3.
(9) Hall, R. H.; Bischofberger, K.; Eitelman, S. J.; Jordaan, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 743. In contrast, however, these same authors report the reaction of stabilized isocyanides with aldonic acid derivatives to give oxazole derivatives: *Ibid.* **1977**, 2236.

Scheme VI[a]



18 22 23

[a] (a) $LiCH_2NC$, THF, DMF, 60%; (b) Me_2SO, $(COCl)_2$, 93%; (c) $CH_3C{\equiv}CMgBr$, THF, 74%; (d) Me_2SO $(COCl)_2$, 85%.

13b (see Experimental Section).[10]

Mechanistically, there are two pathways by which these transformations could proceed. As indicated in Scheme IV, intermediates 11 could collapse directly to oxazolines **12** which upon subsequent aromatization would give the observed products **13** (proton transfers have not been shown for the sake of clarity). In support of this mechanism we cite the known effect of lactone ring size on similar types of reactions,[11] and the fact that oxazolines closely related to **12**, prepared by alternative routes, undergo a rapid base-catalyzed conversion to oxazole alcohols.[12] The rate-determining step in this sequence would thus be the conversion of **11** to **12**. Alternatively, oxazole ring formation could be preceded by a ring opening of **11** to give the highly stabilized enolate **17** (see Scheme V). It has been suggested that in terms of pK_a values this mechanism would proceed in a more favorable direction.[13] If this were the case, however, it would be difficult to rationalize the slow overall conversion of **11** to **13**, since the transformation of **17** to **13** should be an extremely facile process.[8,14] On the basis of our results thus far, however, this mechanism cannot be conclusively ruled out.

Once in hand, we were gratified to find that the conversion of **13a,b** to **7b,c** proceeded exactly according to plan (Scheme IV). Thus, **13a** was cleanly oxidized to the unstable aldehyde **14a** [$Me_2SO/(COCl)_2/NEt_3$,[15] 99%] which was directly condensed with 1.1 equiv of lithiopropyne in THF at −80 °C to give a 75% yield of the diastereomeric alcohols **15a** (9:1 ratio, configurations not assigned). Oxidation to the single acetylenic ketone **16a** then proceeded without event [$Me_2SO/(COCl)_2/NEt_3$,[15] 80%], and finally, **16a** was smoothly converted to the target compound **7b** in refluxing ethylbenzene containing 10 mol % of hydroquinone[5] (30 h, 76% yield). By an identical sequence of steps trans-fused derivative **13b** gave (4aα,8aβ)-3-methyl-5,6,7,8,8a,9-hexahydronaptho[2,3-*b*]-furan-4(4a*H*)-one (**7c**) as a colorless solid, mp 123–124 °C (yields as given). These transformations, we believe, provide overwhelming support for the viability of the bis heteroannulation process.

Finally, we have utilized these same procedures in a novel synthesis of evodone (**23**,[7] Scheme VI). The straightforward nature of this work, beginning with commercially available **18**,[16] requires little further comment. We might only note the overall simplicity of the operations involved.

In closing, the availability of new methodology for the synthesis of complex lactone derivatives[17] convinces us that similar procedures could find wide applicability in the synthesis of furanosesquiterpenes. The total synthesis of ligularone (**7a**) and other members of this class is currently under active investigation.

Experimental Section

Elemental analyses were carried out by the Baron Consulting Co. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E spectrometer. A Varian XL-200 spectrometer, using chloroform-*d* as solvent and Me_4Si as internal standard, was used for the NMR spectra, and IR spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer.

5-[[*cis*-2-(Hydroxymethyl)cyclohexyl]methyl]oxazole (13a). A solution of 1.89 g (12.2 mmol) of lactone **10a**[18] in 10 mL of freshly distilled THF was added dropwise and with efficient stirring to a cooled (−80 °C) suspension of lithiomethyl isocyanide in THF/hexane [prepared by adding 9.0 mL of 1.49 M *n*-BuLi/hexane to a solution of 0.55 g (13.5 mmol, 1.1 equiv) of methyl isocyanide in 55 mL of THF at −80 °C]. After the addition was complete the resultant pale yellow suspension was allowed to warm slowly to room temperature to give, initially, a dark yellow solution and finally an orange heterogeneous mixture. After the mixture was stirred an additional 1 h, sufficient dry DMF (~35 mL) was added to bring all materials back into solution, and the progress of the reaction was followed by TLC (R_f 0.7 for **10a**, silica gel, 2% $MeOH/CH_2Cl_2$; R_f 0.2 for **13a**). After being stirred for a total of 16 h, the reaction mixture was quenched with 771 μL (13.5 mmol, 1.1 equiv) of glacial acetic acid, and the resultant mixture was concentrated to dryness under reduced pressure. The residue was taken up in 100 mL of 5% $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 100 mL) to give 2.26 g of an orange-brown oil, which after chromatography gave 1.53 g (64%) of **13a** as colorless crystals, mp 59–60 °C. The analytical sample was prepared by sublimation at 60 °C (0.001 mmHg): mass spectrum, *m/e* 195 (M^+); IR (CH_2Cl_2) 3330, 1601, 1508 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (m, 8 H), 1.93 (m, 1 H), 2.25 (br m, 1 H), 2.76 (d, J = 7 Hz, $CHCH_2$ α to oxazole, 2 H), 3.72 (m, 2 H), 6.92 (s, 1 H), 7.94 (s, 1 H).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.91; H, 8.38; N, 7.07.

Intermediate 11a. This material was prepared from lactone **10a** by a procedure identical with that described above for **13a**, except that the reaction was quenched with 1.0 equiv of glacial acetic acid immediately after solution was attained. Compound **11a** was obtained as a viscous yellow oil whose NMR and IR spectra indicated less that 2% of open chain isomer **17a** present in solution: mass spectrum, *m/e* 195 (M^+); IR (neat) 3285 (br, OH), 2145 (s, NC) cm^{-1}, no evidence of carbonyl absorption; NMR ($CDCl_3$) δ 0.91–1.61 (br m, 12 H), 3.43 (m, 2 H, CH_2NC), 3.63 (dd, J = 3, 11 Hz, 1 H, CH_2O), 4.05 (dd, J = 3, 11 Hz, 1 H, CH_2O), OH not observed. Compound **11a** decomposed slowly on standing at room temperature but was cleanly converted to **13a** in the presence of base (see above).

5-[[*trans*-2-(Hydroxymethyl)cyclohexyl]methyl]oxazole (13b). This material was prepared from lactone **10b**[19] in 67% yield by a procedure identical with that described above for **13a**: bp 130 °C (0.002 mmHg); mass spectrum, *m/e* 195 (M^+); IR (film) 3330, 1600, 1505 cm^{-1}; NMR ($CDCl_3$) δ 0.68–1.88 (br m, 10 H),

(10) All yields refer to isolated and purified materials, except as noted. All new compounds gave satisfactory elemental analyses and/or spectral data.

(11) Hall, R. H.; Bischofberger, K.; Eitelman, S. J.; Jordaan, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2236.

(12) Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1968**, 1903.

(13) We are grateful to Referee I for several valuable comments.

(14) It is interesting to note that the conversion of **17** to **13** would proceed through an aromatic transition state, while the conversion of **11** to **12** would not.

(15) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(16) We are grateful to the BASF Corp. for a generous gift of **18**.

(17) (a) Baldwin, S. W.; Crimmins, M. T. *Tetrahedron Lett.* **1978**, 4197. (b) Heathcock, C. H.; Wege, P. M.; Clark, R. D. *J. Org. Chem.* **1976**, *41*, 3144. (c) Heathcock, C. H.; Clark, R. D. *Ibid.* **1976**, *41*, 1396. (d) Danishefsky, S. D.; Schuda, P.; Kato, K. *Ibid.* **1976**, *41*, 1081. (e) Grieco, P. A.; Nishiyawa, M.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1976**, *98*, 1612. (f) Heathcock, C. H.; Chavdarian, C. G. *J. Org. Chem.* **1975**, *40*, 2970. (g) Shono, T.; Ohmizu, H.; Kawakami, S.; Sugiyama, H. *Tetrahedron Lett.* **1980**, 5029. (h) Kano, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1980**, *14*, 661.

(18) (a) Stork, G.; Hill, R. K. *J. Am. Chem. Soc.* **1957**, *79*, 499 and references cited therein. (b) See reference 17a.

(19) Granger, R.; Boussinesq, J.; Girard, J.-P.; Rossi, J.-C. *Bull. Soc. Chim. Fr.* **1969**, *8*, 2804.

2.52 (dd, J = 8, 15 Hz, 1 H), 2.84 (dd, J = 4, 15 Hz, 1 H), 3.66 (m, 2 H), 6.77 (s, 1 H), 7.79 (s, 1 H).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.52; H, 8.59; N, 7.37.

5-[(*cis*-2-Formylcyclohexyl)methyl]oxazole (14a). A flame-dried flask under a blanket of dry N_2 was charged with 6.5 mL of dry CH_2Cl_2 (from P_2O_5) and 290 μL (3.3 mmol, 1.3 equiv) of freshly distilled oxalyl chloride.[15] The resultant solution was cooled to −60 °C, and a solution of 473 μL (6.7 mmol, 2.6 equiv) of Me_2SO in 1.5 mL of dry CH_2Cl_2 was added dropwise with stirring. After an additional 5 min a solution of 500 mg (2.56 mmol) of **13a** in 2.5 mL of dry CH_2Cl_2 was added in one portion. The reaction was stirred for 15 min at −60 °C, after which time 1.8 mL (12.8 mmol, 5.0 equiv) of dry TEA was added. After an additional 5 min at −60 °C the reaction mixture was allowed to warm slowly to room temperature. Ten milliliters of H_2O was added, and the organic phase was separated. The aqueous phase was washed with CH_2Cl_2 (2 × 10 mL), and the combined organic layer was washed with 10 mL of saturated brine, dried over $MgSO_4$, filtered, and concentrated. The residue was then taken up in 25 mL of hexane and filtered through Celite. Concentration of this filtrate afforded 492 mg (99%) of aldehyde **14a** of high purity. This material decomposed slowly upon standing and rapidly upon attempted distillation or chromatography: R_f 0.55 (2% MeOH/CH_2Cl_2, silica gel); mass spectrum, m/e 193 (M^+); NMR ($CDCl_3$) δ 0.90–1.97 (br m, 7 H), 2.09 (m, 1 H), 2.37 (m, 1 H), 2.57 (m, 1 H), 2.73 (d, J = 7 Hz, CHC**H**$_2$ α to oxazole, 2 H), 6.73 (s, 1 H), 7.76 (s, 1 H), 9.73 (br s, 1 H).

5-[(*trans*-2-Formylcyclohexyl)methyl]oxazole (14b). This material was prepared from oxazole alcohol **13b** in 95% yield by a procedure identical with that described above for **14a**: R_f 0.62 (2% MeOH/CH_2Cl_2, silica gel); mass spectrum, m/e 193 (M^+); NMR ($CDCl_3$) δ 0.70–1.86 (br m, 8 H), 1.98 (m, 2 H), 2.52 (dd, J = 8, 15 Hz, 1 H), 2.66 (dd, J = 4, 15 Hz, 1 H), 6.75 (s, 1 H), 7.77 (s, 1 H), 9.57 (d, J = 2 Hz, 1 H).

5-[[*cis*-2-(1-Hydroxy-2-butynyl)cyclohexyl]methyl]oxazole (15a). A flame-dried flask under a blanket of dry N_2 was charged with 653 mg (1.05 equiv, 2.59 mmoles) of triphenylmethane and 55 ml of freshly distilled THF (from LAH). The resultant solution was cooled to −80 °C and 1.72 mL (1.05 equiv, 2.59 mmol) of 1.51 M *n*-BuLi/hexane was added dropwise with stirring. After 5 min a stream of propyne gas was slowly bubbled through the solution until the red color dissipated. A solution of 477 mg (2.47 mmol) of aldehyde **14a** in 10 mL of THF was then added dropwise with continued stirring. After the mixture was stirred an addditional 10 min at −80 °C, 10 mL of 2.5% aqueous KH_2PO_4 buffer was added, and the mixture was allowed to warm slowly to room temperature. H_2O (50 mL) was then added, and the organic phase was separated. The aqueous phase was saturated with solid NaCl and extracted with CH_2Cl_2 (2 × 50 mL). The combined layers were dried ($MgSO_4$), filtered, and concentrated to give 1.10 g of crude **15a**. Chromatography of this material on silica gel with 2% MeOH/CH_2Cl_2 as eluant gave 433 mg (75%) of **15a** as a yellow oil: R_f 0.33, 0.40 (1:9 diastereomeric mixture) (2% MeOH/CH_2Cl_2, silica gel); mass spectrum, m/e 233 (M^+); NMR ($CDCl_3$) δ (major isomer) 0.98–1.94 (br m, 9 H), 1.76 (d, J = 1.5 Hz, CCH_3, 3 H), 2.36 (br m, 1 H), 2.62 (d, J = 7 Hz, CH_2 α to oxazole, 2 H), 4.15 (m, 1 H), 6.74 (s, 1 H), 7.76 (s, 1 H).

5-[[*trans*-2-(1-Hydroxy-2-butynyl)cyclohexyl]methyl]oxazole (15b). This material was prepared from oxazole aldehyde **14b** in 81% yield by a procedure identical with that described above for **15a**: yellow viscous oil; R_f 0.40, 0.46 (1:1 diastereomeric mixture) (2% MeOH/$CHCl_3$, silica gel); mass spectrum, m/e 233 (M^+); NMR ($CDCl_3$) δ (0.46 isomer) 0.79–1.98 (br m, 10 H), 1.81 (d, J = 1.5 Hz, 3 H, collapsing to a singlet upon irradiation at 4.69), 2.59 (dd, J = 8, 15 Hz, 1 H), 2.93 (dd, J = 4, 15 Hz, 1 H), 4.69 (m, 1 H, sharpening upon irradiation at 1.81), 6.79 (s, 1 H), 7.80 (s, 1 H).

5-[[*cis*-2-(1-Oxo-2-butynyl)cyclohexyl]methyl]oxazole (16a). This material was prepared from acetylenic oxazole **15a** in 84% yield by a procedure identical with that described above for the conversion of **13a** to **14a**:[15] colorless oil; R_f 0.61 (2% MeOH/CH_2Cl_2, silica gel); mass spectrum, m/e 231 (M^+); IR (film) 2220, 1670, 1600, 1505 cm^{-1}; NMR ($CDCl_3$) δ 0.62–1.92 (br m, 9 H), 1.96 (s, 3 H), 2.36(br m, 1 H), 2.66 (m, CH_2 α to oxazole, 2 H), 6.78 (s, 1 H), 7.80 (s, 1 H); bp 175 °C (0.002 mmHg).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.56; H, 7.33; N, 5.94.

5-[[*trans*-2-(1-Oxo-2-butynyl)cyclohexyl]methyl]oxazole (16b). This material was prepared from acetylenic oxazole **15b** in 91% yield by a procedure identical with that described above for the conversion of **13a** to **14a**:[15] colorless oil; R_f 0.62 (2% MeOH/CH_2Cl_2, silica gel); mass spectrum, m/e 231 (M^+); IR (film) 2210, 1670, 1600, 1505 cm^{-1}; NMR ($CDCl_3$) δ 0.74–1.96 (br m, 9 H), 2.00 (s, 3 H), 2.19 (m, 1 H), 2.48 (dd, J = 8, 15 Hz, 1 H), 2.68 (dd, J = 4, 15 Hz, 1 H), 6.77 (s, 1 H), 7.78 (s, 1 H); bp 170 °C (0.002 mmHg).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.61; H, 7.56; N, 5.81.

(4aα,8aα)-3-Methyl-5,6,7,8,8a,9-hexahydronaptho[2,3-*b*]furan-4(4a*H*)-one (7b). A flame-dried flask under a blanket of dry N_2 was charged with 217 mg (0.94 mmol) of **16a**, 10 mg (0.09 mmol, 0.1 equiv) of hydroquinone, and 26 mL of freshly distilled ethylbenzene (from Na). The reaction was heated under reflux for a total of 36 h. Cooling to room temperature and concentration to dryness afforded 190 mg of residue, which was chromatographed on silica gel with 2% MeOH/$CHCl_3$ as eluant to afford 145 mg (76%) of **7b** as a colorless oil: bp 130 °C (0.002 mmHg); R_f 0.84 (2% MeOH/$CHCl_3$, silica gel); mass spectrum, m/e 204 (M^+); IR (film) 1685, 1610, 1565 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (m, 7 H), 1.95 (br m, 1 H), 2.14 (d, J = 1.5 Hz, 3 H, collapsing to a singlet upon irradiation at 7.03), 2.51 (m, 2 H), 2.87 (m, 2 H), 7.03 (br s, 1 H, collapsing to a sharp singlet upon irradiation at 2.14).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.64; H, 7.69.

(4aα,8aβ)-3-Methyl-5,6,7,8,8a,9-hexahydronaptho[2,3-*b*]furan-4(4a*H*)-one (7c). This material was prepared from acetylenic ketone **16b** in 74% yield by a procedure identical with that described above for the conversion of **16a** to **7b**: colorless solid; mp 123–124 °C; R_f 0.76 (in CH_2Cl_2, silica gel); mass spectrum, m/e 204 (M^+); IR (KBr) 1660, 1595, 1560 cm^{-1}; NMR ($CDCl_3$) δ 0.96–2.06 (br m, 9 H), 2.12 (d, J = 1.5 Hz, 3 H, collapsing to a singlet upon irradiation at 7.02), 2.36 (m, 1 H), 2.51 (dd, J = 11, 17 Hz, 1 H), 2.78 (dd, J = 4, 17 Hz, 1 H), 7.02 (br s, 1 H, collapsing to a sharp singlet upon irradiation at 2.12).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.44; H, 8.10.

5-(2-Methyl-4-hydroxybutyl)oxazole (19). This material was prepared from lactone **18**[16] in 60% yield by a procedure identical with that described above for the conversion of **10a** to **13a**: colorless oil; bp 86 °C (0.02 mmHg); NMR ($CDCl_3$) δ 0.95 (d, J = 6 Hz, 3 H), 1.18–1.78 (br m, 2 H), 1.80–2.30 (br m, 1 H), 2.57–2.70 (m, 2 H), 2.90 (br s, 1 H), 3.66 (t, J = 6 Hz, 2 H), 6.77 (s, 1 H), 7.78 (s, 1 H).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.94; H, 8.34; N, 9.03. Found: C, 61.69; H, 8.19; N, 9.24.

5-(2-Methyl-3-formylpropyl)oxazole (20). This material was prepared from oxazole alcohol **19** in 93% yield by a procedure identical with that described for the conversion of **13a** to **14a**: colorless unstable oil; mass spectrum, m/e 153 (M^+); NMR ($CDCl_3$) δ 1.02 (d, J = 6 Hz, 3 H), 2.20–2.60 (m, 3 H), 2.68 (d, J = 7.2 Hz, 2 H), 6.78 (s, 1 H), 7.78 (s, 1 H), 9.76 (br s, 1 H).

5-(2-Methyl-4-hydroxy-5-heptynyl)oxazole (21). Propyne gas was slowly bubbled into a stirring solution of 0.60 mL of 1.97 M C_2H_5MgBr in 10 mL of dry THF under an atmosphere of dry N_2. After 15 min the generated propynylmagnesium bromide was added dropwise to a solution of 105 mg (0.69 mmol) of **20** in 10 mL of dry THF kept at 0 °C. After the addition was complete, the reaction mixture was stirred for an additional 20 min at 0 °C and then quenched with 5 mL of a saturated solution of NH_4Cl. The resulting mixture was extracted with ether, dried ($MgSO_4$), and concentrated under reduced pressure to afford 145 mg of a yellow oil. Chromatography (40% acetone/petroleum ether) of this material gave 98 mg (74%) of **21** as a pale yellow oil: NMR ($CDCl_3$) δ 0.88 (m, 3 H), 1.32–1.72 (br m, 3 H), 1.78 (d, J = 2.2 Hz, 3 H), 2.02–2.18 (m, 1 H), 2.44–2.74 (m, 2 H), 4.38 (br s, 1 H), 6.82 (s, 1 H), 7.83 (s, 1 H).

5-(2-Methyl-4-oxo-5-heptynyl)oxazole (22). This material was prepared from acetylenic oxazole **21** in 85% yield by a procedure identical with that described for the conversion of **13a** to **14a**:[15] colorless oil; bp 72 °C (0.05 mmHg); NMR ($CDCl_3$) δ 0.92

(d, J = 6 Hz, 3 H), 1.96 (s, 3 H), 2.30–2.52 (m, 3 H), 2.52–2.66 (m, 2 H), 6.82 (s, 1 H), 7.82 (s, 1 H).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.33. Found: C, 68.90; H, 6.51; N, 7.49.

Evodone (23). To a suspension of 5 mg (0.05 mmol) of hydroquinone in 20 mL of freshly distilled ethylbenzene in a 25-mL, round-bottomed flask was added 60 mg (0.30 mmol) of acetylenic ketone **22**. The resulting solution was refluxed in the absence of light and under an atmosphere of dry N_2 for a period of 96 h. The ethylbenzene was then removed under reduced pressure to afford ~70 mg of a dark brown oil. Thick-layer chromatography (40% acetone/petroleum ether, R_f 0.65) of this material afforded 39 mg (76%) of **23** as a colorless crystalline solid. Recrystallization from MeOH/H_2O gave colorless needles, which after sublimation (0.015 mmHg, 25 °C) had a melting point of 70–71 °C (lit.[7] mp 73 °C): IR ($CHCl_3$) 3000, 2960, 1662, 1560, 1440, 1430, 1410, 1388, 1362, 1080, 1045 cm^{-1}; UV (MeOH) λ_{max} 265 nm (lit.[7] 265 nm); NMR ($CDCl_3$) δ 1.09 (d, J = 6 Hz, 3 H), 1.58 (m, 1 H), 2.14 (d, J = 1.3 Hz, 3 H), 2.30–2.58 (m, 3 H), 2.88 (dd, J = 4, 13 Hz, 1 H), 7.08 (br s, collapsing to a sharp singlet upon irradiation at 2.14, 1 H); mass spectrum, m/e 164 (M^+); mp (2,4-DNPH) 260–262 °C (lit.[20] mp 258–260 °C).

Acknowledgment. Financial support of this work by the National Science Foundation (Grant No. CHE-7800633) is gratefully acknowledge. The Varian XL-200 spectrometer used in this work was financed in part by the National Science Foundation (Grant No. CHE-7908593), the Dreyfus Foundation, and Wesleyan University. D. G.W. was the recipient of a Sigma Xi Grant in Aid of Research during the course of this work. I.M.A.O. was the recipeint of an America-Mideast Educational and Training Fellowship.

Registry No. 7b, 76879-68-0; **7c**, 76879-69-1; **10a**, 24112-69-4; **10b**, 18335-58-5; **11a**, 76900-27-1; **13a**, 76879-70-4; **13b**, 76879-71-5; **14a**, 76879-72-6; **14b**, 76879-73-7; **15a** (isomer 1), 76879-74-8; **15a** (isomer 2), 76945-53-4; **15b** (isomer 1), 76945-54-5; **15b** (isomer 2), 76945-55-6; **16a**, 76879-75-9; **16b**, 76879-76-0; **18**, 1121-84-2; **19**, 76879-77-1; **20**, 76879-78-2; **21**, 76879-79-3; **22**, 76879-80-6; **23**, 529-63-5; **23** DNP, 76879-81-7; lithiomethyl isocyanide, 33742-77-7; propynyl bromide, 2003-82-9.

(20) Stetter, H.; Lauterbach, R. *Chem. Ber.* **1960**, *93*, 603.

Synthesis of *N*-(Tosylmethyl)carbodiimides and Their Application in the Synthesis of 2-Amino-1,3-oxazoles from Aldehydes

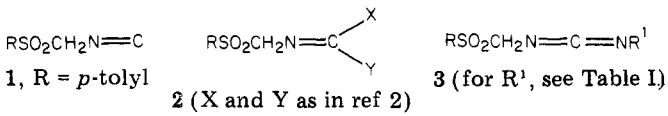
Albert M. van Leusen,* Hans J. Jeuring, Jurjen Wildeman, and Simon P. J. M. van Nispen

Department of Organic Chemistry, Groningen University, Nijenborgh 16, 9747 AG Groningen, The Netherlands

Received October 22, 1980

A series of *N*-(tosylmethyl)carbodiimides ($TosCH_2N{=}C{=}NR^1$, **3**) have been prepared from the corresponding thioureas. Carbodiimides **3** with R^1 = triphenylmethyl or *tert*-butyl are useful synthons in a new one-step synthesis of 2-(alkylamino)-1,3-oxazoles **10** from aromatic aldehydes. Acid-induced removal of the triphenylmethyl group from **10** gives 2-amino-1,3-oxazoles (**11**).

The successful use of tosylmethyl isocyanide (TosMIC, **1**) in organic synthesis[1] has stimulated us to investigate



1, R = *p*-tolyl

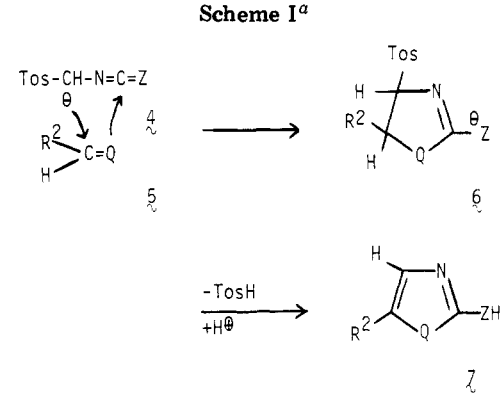
2 (X and Y as in ref 2)

3 (for R^1, see Table I)

other potential synthons operating on a comparable basis. In previous papers from this laboratory the preparation of a series of (sulfonylmethyl)imino derivatives **2** and their application to the synthesis of azoles have been discussed.[2] We now report the synthesis of a number of *N*-(tosylmethyl)carbodiimides **3** and their use in the preparation of 2-amino-1,3-oxazoles.

When applied to the synthesis of azoles, the essentials of TosMIC chemistry[1] are given in Scheme I: attack of TosMIC anion (**4**, Z = void) at the electrophilic end of certain carbon–carbon or carbon–heteroatom multiple bonds (**5**) and ring closure through the isocyano carbon (to **6**), followed by in situ elimination of *p*-toluenesulfinic acid (TosH) to give **7**.

Scheme I[a]



[a] For TosMIC: Z = void, Q = O, NR, S, CHCOOR, etc.; Tos = *p*-tolylsulfonyl.[1] Present paper: Z = NR^1 (R^1, Table I) and Q = O (R^2, Table II).

It is the purpose of this paper to show that the central carbodiimido carbon of *N*-(tosylmethyl)carbodiimides **3** can fulfil a role similar to the isocyano carbon of TosMIC. To that end it was necessary to develop a synthesis for the previously unknown (tosylmethyl)carbodiimides **3**.[3,4]

(1) A brief review: van Leusen, A. M. *Lect. Heterocycl. Chem.* **1980**, *5*, S111 (a supplementary issue of volume 17 of *J. Heterocycl. Chem.*).

(2) (a) Houwing, H. A., Wildeman, J.; van Leusen, A. M. *Tetrahedron Lett.* **1976**, 143. (b) Houwing, H. A., Ph.D. Thesis, Groningen University, 1978.

0022-3263/81/1946-2069$01.25/0