Tetrahedron Vol. 47, No 36, pp 7713-7718, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

Synthesis of 2*H* ,4*H* ,9b*H* -Furo[3,2-*c*][1]benzopyrans by a new Intramolecular Cycloaddition of a Carbonyl Ylide to an Acetylene

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(*Received in UK* 8 *May* 1991)

Key words intramolecular 1,3-dipolar cycloaddition, carbonyl ylide, acetylene, furobenzopyran

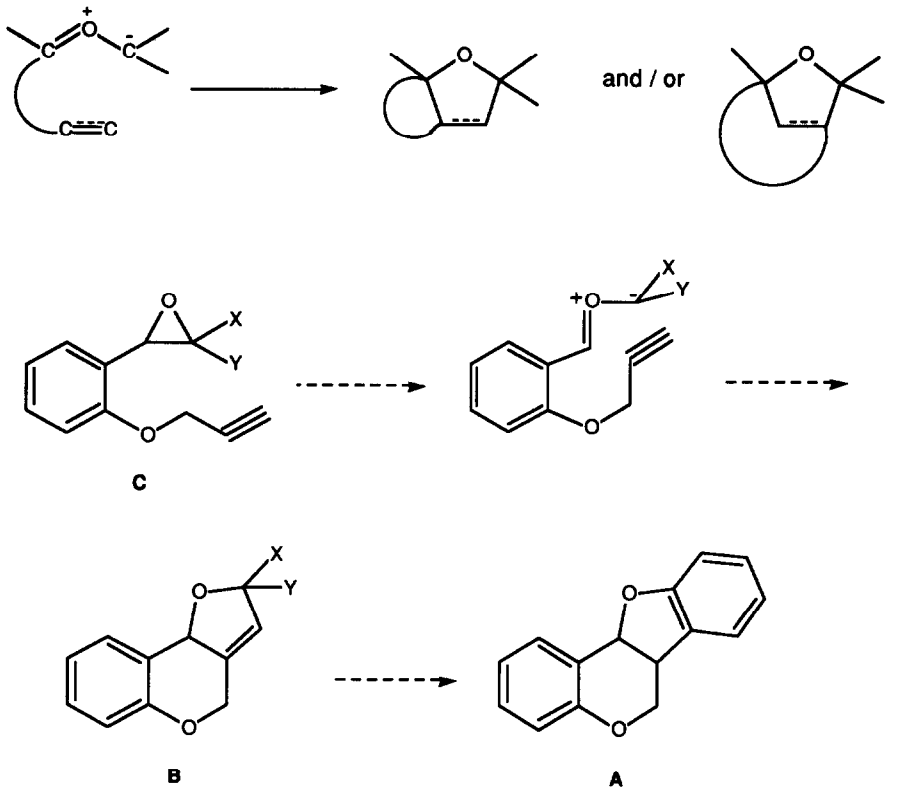
Abstract - Thermal treatment of oxiranes **1** and **4** affords 2*H* ,4*H* ,9b*H* -furo[3,2-*c*][1]benzopyrans **5** and **6** through an intra-molecular 1,3-dipolar cycloaddition between the carbonyl ylide, generated by ring opening of the oxirane, and the acetylene moiety

INTRODUCTION

In the last decade, intra- and intermolecular 1,3-dipolar cycloaddition has provided one of the most powerful tools for the synthesis of complex skeletons possesing 5-membered heterocycles, because of the high level of regio- and stereochemical control [1] The chemistry of carbonyl ylides as 1,3-dipoles has been extensively studied for the preparation of differently substituted tetrahydrofurans Several methods have been described for the generation of this dipole the thermal or photochemical ring opening of oxiranes,[2-5] thermolysis of oxadiazolines,[6] carbon dioxide elimination from dioxolanones,[7] carbon monoxide extrusion from oxetanones,[8] and the addition of carbenes to carbonyl compounds [9-16]

The intramolecular cycloaddition of a properly functionalized molecule bearing a carbonyl ylide and a dipolarophile[4,10] represents a general method for the simultaneous formation of two fused heterocycles one 5-membered tetrahydrofuran and the size of the other depending on the length of the tether (Scheme 1) When dipole and dipolarophile are joined through a three or four-atom chain the yields in bicyclic compounds are usually high [1,4,10] Although the use of an olefin as dipolarophile in the intramolecular cycloadditions with carbonyl ylides has been extensively studied by W Eberbach and co-workers[4] during the 80's, no example using an alkyne has been described The presence of an acetylenic bond as dipolarophile would give rise to the formation of a dihydrofuran, an unsaturated heterocycle, that would easily allow further chemical transformations

In relation with our interest in the synthesis of pterocarpans, **A**, we have developed a new synthesis of 2*H* ,4*H* ,9b*H* -furo[3,2-*c*][1]benzopyrans, **B**, based on the thermal opening and intramolecular cyclization of the acetylenic oxiranes **C** Although many synthesis of 4*H* -furo[3,2-*c*][1]benzopyran-4-ones are known in the literature, there are only three methods described for the preparation of the corresponding furobenzopyrans[4,17] and to the best of our knowledge this is the first synthesis of the unsaturated heterocyclic system **B**



Scheme 1

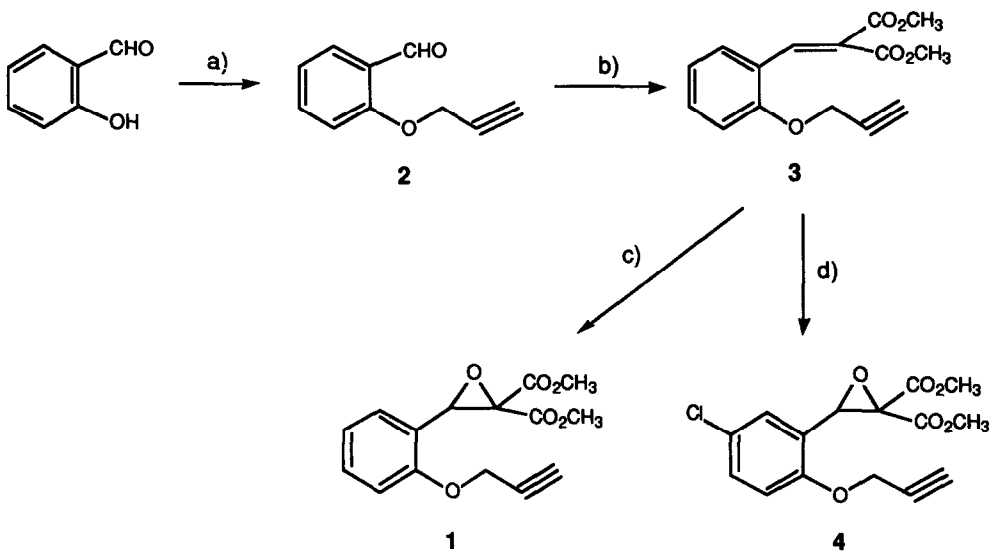
RESULTS AND DISCUSSION

Only good yields in the generation of carbonyl ylides by thermolysis of oxiranes are obtained when geminal electron-withdrawing groups (X and Y) are present in the oxiranic ring, that can stabilize the negative charge of the intermediate ylide We therefore started our studies with oxirane **1**, whose synthesis is indicated in Scheme 2

Aldehyde **2** was prepared from salicylaldehyde and propargylbromide using phase transfer catalysis in almost quantitative yield [18,19] Its reaction with dimethyl malonate under Knövenagel condensation conditions afforded the new olefin **3** in 81% yield The presence of the acetylenic proton was confirmed by the ir spectrum (3250 and 2110 cm^{-1}) and the triplet at δ 2 34 (J=2 4 Hz) in the pmr spectrum The olefinic proton is strongly deshielded, its chemical shift being δ 8 09

The epoxidation of electron-withdrawing *gem* -disubstituted olefins is reported in the literature[20] using sodium hypochlorite at neutral pH The reaction of **3** with NaClO in acetonitrile/water afforded a white solid with mp 76-77°C identified as 1,1-bis(methoxycarbonyl)-2-[5-chloro-2-(2-propynyloxy)phenyl]oxirane, **4** (47%

yield) by its analytical data Its pmr spectrum in $CDCl_3$ presented a signal at δ 4 73-4 77 whose intensity corresponded to three hydrogen atoms, indicating the formation of the oxirane, but the complex absorption at δ 6 84-7.40 presented the same intensity, *i e* three protons The chlorination of the aromatic ring was confirmed by the mass spectrum (*m/e* =326-324 for $C_{15}H_{13}ClO_6$). In the literature we found that phenols can be chlorinated in the darkness with hypochlorite [21] It remained to establish the position of the chlorine atom and this was accomplished by running the pmr spectrum in hexadeuteriobenzene in this solvent the aromatic absorptions were two doublets (δ 6 43 with J=8 6 Hz and 7 51 with J=2 4 Hz) and a double doublet (δ 7 00) These multiplicities and coupling constant values are only consistent with the chlorine atom in *meta* or *para* position respect



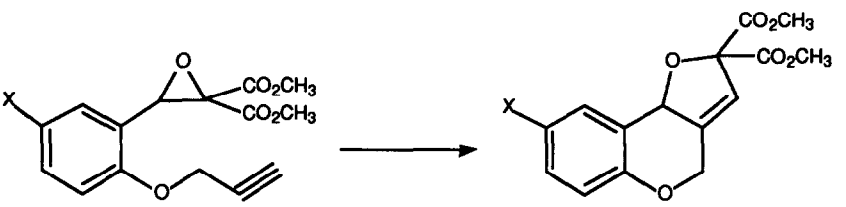
a) $BrCH_2C{\equiv}CH$, NaOH, n-Bu_4NHSO_4 cat , CH_2Cl_2/H_2O
b) $CH_2(CO_2CH_3)_2$, piperidine cat , C_6H_6
c) NaClO, n-Bu_4NHSO_4 cat , CH_2Cl_2/H_2O
d) NaClO, pH 7-8, CH_3CN/H_2O

Scheme 2

to the phenolic oxygen atom, but the first one should be rejected based on mechanistic considerations The oxiranic proton (δ 4 89) and the methylene protons (δ 4 13) were no longer isochronous in the C_6D_6 pmr spectrum

When we changed the solvent to a methylene chloride-water mixture using the technique of phase transfer catalysis[22] the aromatic chlorination reaction was no longer observed and the desired oxirane **1** was isolated with a satisfactory yield The explanation to this different behaviour of the oxidizing reagent may be found in the reduced exposure of the organic substrate to the hypochlorite when using a two-phase system.The thermal

generation of carbonyl ylides requires temperatures over 110°C[2-4] and we choosed chlorobenzene as solvent for our intramolecular 1,3-dipolar cycloaddition Heating a solution of **1** at 160°C in a pressure-resistant vessel for 13 hours (disappearance of starting material) allowed the isolation (76% yield) of a white solid (mp 114-115°C) that was identified by its spectroscopic data and elemental analysis as the furo[3,2-*c*][1]benzopyran **5** (Scheme 3) The reaction in less polar solvents as diglyme or 1,3-dichlorobenzene afforded also heterocycle **5**, but in lower yields (30-40%) The olefinic and the methinic protons were unfortunately isochronous in the pmr spectrum in $CDCl_3$ These two protons absorbed separately (δ 5 77 and 5.90) in the hexadeuteriobenzene solution, where the non-equivalent methylenic protons absorbed as two doublets at d 4 10 and 4 35



1, X = H
4, X = Cl

5, X= H
6, X= Cl

Scheme 3

The same reaction conditions were applied to **4**, but 21 hours were now needed for the disappearance of the starting material Furobenzopyran **6** was isolated in 51% yield as a pale yellow solid The yields in diglyme and 1,3-dichlorobenzene were again lower The aromatic region of the pmr spectrum in $CDCl_3$ presented two doublets (δ 6 74 and 7 43) and a double doublet (δ 7 12), which confirmed the halogen position In this case the olefinic and the methinic protons were isochronous in $CDCl_3$ and C_6D_6 The presence of the electron-withdrawing chlorine atom, although not directly attached to the oxirane ring, seems to slow the conrotatory ring opening

In conclusion, a new and easy access to substituted 2*H* ,4*H* ,9b*H* -furo[3,2-*c*][1]benzopyrans, potential intermediates to pterocarpans from intramolecular cyclization of carbonyl ylides to acetylenes has been achieved

EXPERIMENTAL SECTION

The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer The nmr spectra were recorded on a Bruker WP80SY spectrometer, chemical shifts are given in ppm relative to TMS (δ values) The mass spectra were run on a Hewlett-Packard 5985B spectrometer, only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments

2-(2-Propynyloxy)benzaldehyde , **2**

This product was prepared by a previously reported procedure [18,19]

Dimethyl 2-(2-propynyloxy)benzylidenemalonate , **3**

A solution of **2** (20 0 g, 0 12 mol), dimethyl malonate (19 8 g, 0 15 mol), piperidine (2 mL), and a catalytic amount of benzoic acid in benzene (40 mL) was heated in a Dean-Stark at 105-110°C After quantitative separation of water (2 3 mL, 0 12 mol) the solvent was evaporated and crude **2** solidified Recrystallization from methylene chloride-pentane afforded 26 8 g (0 098 mol, 81% yield) of **3** mp 73-75°C, ir (KBr) 3250, 2110,

1725, 1700, 1625 cm^{-1}, pmr ($CDCl_3$) 2 34 (t, J=2 4 Hz, 2H), 3 78 (s, 3H), 3 84 (s, 3H), 4 75 (d, J=2 4 Hz, 2H), 6 84-7.50 (m, 4H), 8 09 (s, 1H); cmr ($CDCl_3$) 52 2, 52.4, 56.4, 76.4, 78.1, 112 9, 121.9, 123 2, 126.1, 129.3, 131.8, 138.7, 156 1, 164 6, 166 9, ms *m/e* 274 (M^+, 45), 243 (24), 219 (98), 215 (82), 211 (25), 210 (31), 199 (28), 184 (24), 176 (22), 173 (76), 155 (46), 146 (29), 145 (100), 142 (37), 131 (23), 128 (30), 127 (21), 101 (21), 89 (79), 77 (24), 63 (38), 59 (39) Anal Calcd for $C_{15}H_{14}O_5$ C, 65 69, H, 5 15 Found C, 65 86, H, 5 29

1,1-Bis(methoxycarbonyl)-2[2-(2-propynyloxy)phenyl]oxirane , **1**

A mixture of **3** (1 0 g, 3 6 mmol), tetrabutylammonium hydrogen sulphate (50 mg), methylene chloride (13.6 mL), and 1.34 N sodium hypochlorite solution (13.6 mL, 18.2 mmol) was stirred for 26 hours at room temperature Water (50 mL) was added and the mixture was extracted with dichloromethane (3x50 mL) The organic layer was dried over anhydrous sodium sulphate and evaporated to afford 1 08 g of a yellow oil, that crystallized on standing Recrystallization from methanol allowed the isolation of 606 mg (58% yield) of pure **1** as a white solid. mp 65-66°C, ir (KBr) 3240, 1730-1710 cm^{-1}, pmr ($CDCl_3$) 2 49 (t, J=2 4 Hz, 1H), 3 55 (s, 3H), 3 88 (s, 3H), 4 78 (br s, 3H), 6.83-7 15 (m, 4H), pmr (C_6D_6) 1 97 (t, J=2 4 Hz, 1H), 3 16 (s, 3H), 3 25 (s, 3H), 4 19 (d, J=2 4 Hz, 2H), 5 03 (s, 1H), 6 56-7 59 (m, 4H), cmr ($CDCl_3$) 52 1, 53 0, 56 2, 58 8, 62 4, 75 7, 78 1, 112 1, 121 1, 121 3, 126 1, 129 7, 156 2, 163 8, 165 6; ms *m/e* 290 (M^+, 4), 274 (1), 259 (2), 175 (100), 115 (52), 105 (24), 77 (36), 59 (25), 51 (27) Anal Calcd for $C_{15}H_{14}O_6$ C, 62 07, H, 4 86 Found C, 62 23· H, 4 96

1,1-Bis(methoxycarbonyl)-2-[5-chloro-2-(2-propynyloxyphenyl)]oxirane, **4**

To a well stirred solution of **3** (1 01 g, 3 6 mmol) in acetonitrile (15 mL) in a 150 mL baker glass, a 1 34 N sodium hypochlorite solution (26 8 mL, 36 0 mmol) was added during 2 hours During this process the mixture was kept at pH 7-8 (pHmeter) by controled addition of 2 N sulphuric acid Water (100 mL) was added and the mixture was extracted with dichloromethane (3x100 mL) The organic layer was dried over anhydrous sodium sulphate and evaporated to afford a white solid (1 14 g) Recrystallization from methanol allowed the isolation of 560 mg (47% yield) of pure **4** mp 76-77°C, ir (KBr) 3290, 1745 cm^{-1}, pmr ($CDCl_3$) 2 55 (t, J=2 4 Hz, 1H), 3 60 (s, 3H), 3 85 (s, 3H), 4 75 (br s, 3H), 6 84-7 40 (m, 3H), pmr (C_6D_6) 2 0 (t, J=2 4 Hz, 1H), 3 13 (s, 3H), 3 22 (s, 3H), 4 13 (d, J=2 4 Hz, 2H), 4 89 (s, 1H), 6 43 (d, J=8 6 Hz, 1H), 7 00 (dd, J=8 6 Hz, J'=2 4 Hz, 1H), 7 51 (d, J=2 4 Hz, 1H), cmr ($CDCl_3$) 52 3, 53 2, 56 7, 58 3, 62 4, 76 2, 77 8, 113 7, 123 4, 126 4, 126 7, 129 6, 154 8, 163 6, 165 4, ms *m/e* 326-324 (M^+, 5, 12), 262 (3), 260 (9), 211 (23), 209 (67), 179 (26), 167 (24), 139 (28), 115 (26), 111 (35), 75 (45), 59 (100) Anal Calcd for $C_{15}H_{13}ClO_6$ C, 55 49, H, 4 03 Found C, 55 73, H, 4 16

Dimethyl 2H,4H,9bH-furo[3,2-c][1]benzopyran-2,2-dicarboxylate , **5**

A solution of **1** (3 36 g, 11 6 mmol) in chlorobenzene (80 mL) was heated in a pressure-resistant vessel at 160°C during 13 hours Elimination of the solvent by vacuum distillation afforded a yellow solid Recrystallization from methanol gave **5** (2 56 g, 76% yield) as a white solid mp 114-115°C, ir (KBr) 3110, 2960, 1745, 1725 cm^{-1}, pmr ($CDCl_3$) 3 71 (s, 3H), 3 80 (s, 3H), 4 80 (br s, 2H), 5 80-6 00 (br s, 2H), 6 68-7 50 (m, 4H), pmr (C_6D_6) 3 40 (s, 3H), 3 71 (s, 3H), 4 10 (d, J=13 5 Hz, 1H), 4 35 (d, J= 13 5 Hz, 1H), 5 77 (br s, 1H), 5 90 (br s, 1H), 6 62-7 68 (m, 4H), cmr ($CDCl_3$) 52 8, 52 9, 63 1, 81 6, 94 8, 116 6, 119 4, 121 4, 124 6, 126 5, 129 1, 139 6, 152 6, 167 4, 168 4, ms *m/e* 290 (M^+, 69), 231 (27), 172 (15), 171 (100), 115 (22), 59 (12) Anal Calcd for $C_{15}H_{14}O_6$ C, 62 07, H, 4 86 Found C, 62 36, H, 4 93

Dimethyl 8-chloro-2H,4H,9bH-furo[3,2-c][1]benzopyran-2,2-dicarboxylate, ***6***

A solution of **4** (0 98 g, 3 0 mmol) in chlorobenzene (17 mL) was heated in a pressure-resistant vessel at 160°C during 21 hours Elimination of the solvent by vacuum distillation afforded a yellow solid

Recrystallization from methanol gave **6** (0.505 g, 51% yield) as a pale yellow solid· mp 109-110°C, ir (KBr) 3100, 2960, 1740 cm^{-1}, pmr ($CDCl_3$) 3 77 (s, 3H), 3 86 (s, 3H), 4.86 (br s, 2H), 5 95 (br, s, 2H), 6 74 (d, J=8 6 Hz, 1H), 7.12 (dd, J=8 6 Hz, J'=2 4 Hz, 1H), 7 43 (d, J=2 4 Hz, 1H), pmr (C_6D_6) 3 18 (s, 3H), 3 37 (s, 3H), 4 00 (d, J=13 5 Hz, 1H), 4 20 (d, J=13 5 Hz, 1H), 5 68 (br s, 2H), 6 49 (d, J=8.6 Hz, 1H), 6 86 (dd, J=8 6 Hz, J'=2 4 Hz, 1H), 7 55 (d, J=2.4 Hz, 1H), pmr ($CDCl_3$) 52 9, 53 0, 63 3, 81 1, 94 9, 118 1, 120 0, 126 0, 126 2, 126 4, 129 1, 138 7, 151 2, 167 2, 168 1, ms *m/e* 326-324 (M^+, 2, 5), 265 (15), 207 (25), 205 (100), 115 (48), 59 (55) Anal Calcd for $C_{15}H_{13}ClO_6$ C, 55.49, H, 4 03 Found C, 55 28, H, 4.10.

Acknowledgments.- Financial support from "Comisión Asesora de Investigación Científica y Técnica" project nº PB89-0287 is gratefully acknowledged.

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