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단 신

다이아조 메탄에 의한 γ-Alkoxy-α,β-unsaturated Acid의 고리첨가반응

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Cycloaddition of γ-Alkoxy-α,β-unsaturated Acids with Diazomethane

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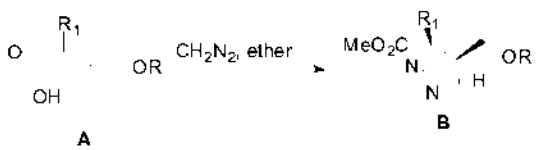
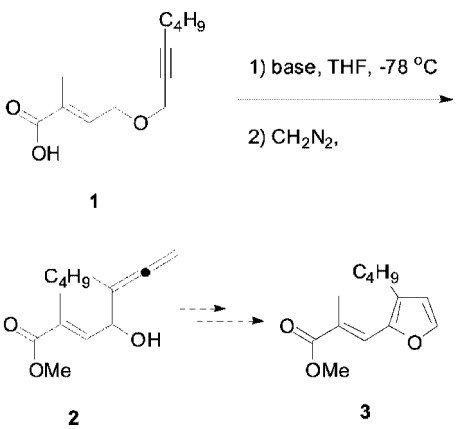
주제어: 다이아조메탄, 고리첨가반응, 피라졸린

Keywords: Diazomethane, Cycloaddition, Pyrazoline

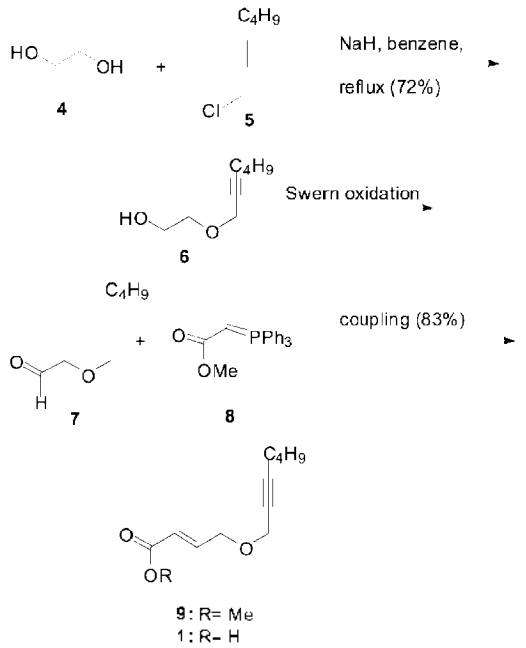
Diazomethane is known to undergo [3+2] addition reaction with alkenes and alkynes to give pyrazolines and pyrazole respectively.[1] The reaction proceeds rapidly with electron-deficient alkenes and strained alkenes. The recent applications of the [3+2] cycloaddition to natural products bearing cyclic α,β-unsaturated ester were reported[2] The reaction is controlled by FMO consideration: the HOMO of the diazomethane and the LUMO of the alkenes serving as a predominant interaction.[3] The corresponding pyrazolines are most often used as precursors to cyclopropanes by either thermal or photochemical exclusion of N_2.[1] To our knowledge the cycloaddition of γ-alkoxy-α,β-unsaturated acids with diazomethane to alkoxy pyrazoline such as **B** has been prepared before in a limited scope.[5] Therefore it is our intention to report the examples of the preparation in this paper.



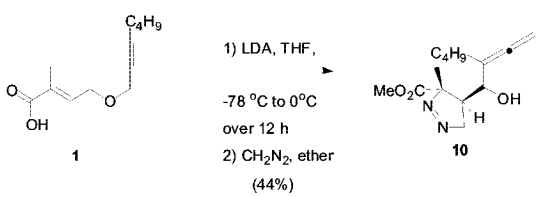
This reaction was observed when we investigated [2,3] Wittig rearrangement[6] of dianion of propargyloxy-α,β-unsaturated caboxylic acid to provide allenol ester such as **2** to prepare 2,3-substituted furano compounds which could be applied to the synthesis of furano natural products.[7]



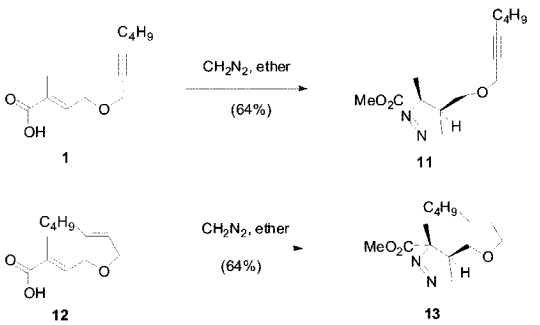
The γ-propargyloxy-α,β-unsaturated acid was prepared as followings: the substitution of sodium hydroxyethylalkoxide with the propargylic chloride generated from the corresponding propargylic alcohol by Collington-Meyer chlorination[8] gave β-alkoxy alcohol **6**. The alcohol was oxidized by Swern condition. The following coupling of the aldehyde with the ylide **8** gave γ-alkoxy-α,β-unsaturated acid after the treatment with LiOH in the mixture of methanol and water.



The planned Wittig reaction of **1** gave us an unknown substance which was identified as allene pyrzoline **10** by a three fold reaction pathway: Wittig reaction, methylation and [3+2] dipolar cycloaddition with generated diazomethane. Therefore the pyrazoline **10** was obtained in 44% yield.



The direct addition of excess diazomethane in ether to γ-propargyloxy-α,β-unsaturated acid and allyloxy-α,β-unsaturated acid gave rise to the corresponding pyrazolines in 64% yields respectively. The compound **12** possessing an allyloxy system could be prepared in the silmilar steps starting from 2-heptenyl chloride in excellent yields.[9]



The pyrazoline **11** was fully identified by the following spectroscopic method: a decoupling experiment was carried. The irradiation of methine H caused simplification of ABX system of propargylic methylene and pyrazoline methylene peaks to AB system (*Fig.* 1). Mass spectrum shows 2 nitrogens and also CH_2N_2 fragmentation was observed.

In conclusion, we have demonstrated the cycloaddition of γ-alkoxy-α,β-unsaturated acids with diazomethane to afford the alkoxypyrazoline system. The synthetic application of the prazolines will be reported in due course.

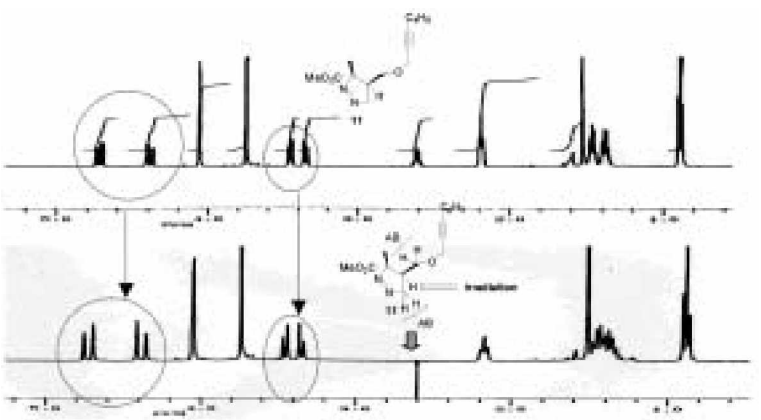


Fig. 1. ^{1}H NMR spectrum (500 MHz) and the decoupling experiment (300 MHz) of the pyrazoline **11**.

EXPERIMENTALS

2-Hept-2-ynyloxy-ethanol (6)

To a suspension of 779 mg (32.1 mmol) of NaH in 20 mL of benzene was added 22.3 mL (306 mmol) of ethylene glycohol dropwise at 0 °C. The solution was refluxed for 2 hrs and cooled to room temperature. To the solution was added 4.0 g (30.6 mmol) of the chloride **5** in 5 mL of benzene. The solution was refluxed for 4 hrs and cooled to room temperature. Water was added and the aqueous layer was separated and extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 50% ethylacetate in hexanes gave 3.43 g(72%) of the alcohol **6**: IR (film) υ 3417, 2934, 2864, 1638, 1354 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (2H, t, J=2.0 Hz, propargylic Hs), 3.73 (2H, brt, HOC**H**$_2$-), 3.59 (2H, brt, HOCH$_2$C**H**$_2$-), 2.20 (1H, tt, J=4.9, 2.0 Hz, propargylic Hs), 2.09 (1H, brt, -OH), 1.52-1.32 (4H, m, $CH_3(CH_2)_2$-), 0.88 (3H, t, J=7.2 Hz, -CH_3) ppm.

4-Hept-2-ynyloxy-2-methyl-but-2-enoic acid methyl ester (9) and 4-Hept-2-ynyloxy-2-methyl-but-2-enoic acid (1)

To a solution of 1.58 mL (18.2 mL) of oxalyl chloride in 20 mL of CH_2Cl_2 was added 2.58 mL (3.63 mmol) of DMSO at -78 °C. The solution was stirred for 10 min and then added 1.89 g (12.1 mmol) of the alcohol **6** in 5 mL of CH_2Cl_2. The resultant white emulsion was stirred for 40 min and 7.43 g (21.3 mmol) of 2-(triphenylphosphanylidene)-propionic acid methyl ester[11] was added. The solution was warmed to room temperature and stirred overnight. Water was added and the organic layer was extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% ethyl acetate in hexanes gave 2.24 g (83%) of the ester **9**: IR (film) υ 2956, 2862, 2360, 1720, 1656, 14536, 1253, 1136, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (1H, t, J=6.1 Hz, vinyl H), 4.21 (2H, d, J=6.1 Hz, allylic Hs), 4.13 (2H, t, J=2.2 Hz, propargylic Hs), 3.73 (3H, s, -OCH_3), 2.21 (2H, tt, J= 6.9, 2.2 Hz, propargylic Hs) 1.84 (3H, s, vinyl CH_3), 1.50-1.35 (4H, $CH_3(CH_2)_2$-), 0.89 (3H, t, J=7.1 Hz, -CH_3) ppm. The resultant ester was dissolved in the mixture of methanol-water and treated with LiOH-H_2O. The solution was stirred overnight and quenched with 3% HCl. The aqueous layer was separated and extracted with CH_2Cl_2 three times and the extracts were washed with saturated $NaHCO_3$ and then with brine. The residue was concentrated under reduced pressure to afford the acid **1** quantitatively.

The IR shows the broad carboxylic OH at 3443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (1H, t, J= 6.1 Hz, vinyl H), 4.21 (2H, d, J=6.1 Hz, allylic Hs), 4.13 (2H, t, J=2.2 Hz, propargylic Hs), 2.21 (2H, tt, J=6.9, 2.2 Hz, propargylic Hs) 1.84 (3H, s, vinyl CH_3), 1.50-1.35 (4H, m, $CH_3(CH_2)_2$-), 0.89 (3H, t, J=7.1 Hz, -CH_3) ppm.

4-(2-Butyl-1-hydroxy-buta-2,3-dienyl)-3-methyl-4,5-dihydro-3H-pyrazole-3-carboxylic acid methyl ester (10)

To a solution of 0.096 mL (0.95 mmol) of diisopropylamine in 1 mL of THF was added 0.380 mL of 2.5 M n-BuLi in hexanes at 0 °C. The solution was stirred for 10 mins and cooled to -78 °C and then added 80 mg (0.38 mmol) of the acid **1** in 1 mL of THF dropwise. The solution was gradually warmed to room temperature over 12 hrs and then quenched with 1 N HCl. The aqueous solution was separated and extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford 71 mg of a mixture. The residue was diluted in ether and the solution was treated with an ethereal solution of diazomethane. The excess diazomethane was quenched with acetic acid and the resultant solution was concentrated under reduced pressure. The residue was chromatograped on silica gel. Elution with 10% ethyl acetate in hexanes gave 44 mg (44%) of the pyrazoline **10**: IR (film) υ 3422, 2956, 1955, 1738, 1560, 1435, 1247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.95 and 4.93 (2H, d, J=2.0 Hz, allenic Hs), 4.62 and 4.52 (2H, ABX, J_{AB}=18.0, J_{AX} =8.4, J_{BX}=5.8 Hz, -N_2CH_2-), 3.99 (1H, brs, -C**H**OH), 3.71 (3H, s, -OCH_3), 2.60 (1H, m, methine H), 2.20

(1H, brs, -OH), 1.92 (2H, m, allylic CH_2), 1.66(3H, s, -CH_3), 1.50-1.20 (4H, m, -$(CH_2)_2$-), 0.87 (3H, t, J=6.0 Hz, -CH_3) ppm.

4-Hept-2-ynyloxymethyl-3-methyl-4,5-dihydro-3H-pyrazole-3-carboxylic acid methyl ester (11)

To a solution of 60 mg (0.27 mmol) of the acid **1** in THF was treated with an ethereal solution of diazomethane. The excess diazomethane was quenched with acetic acid and the resultant solution was concentrated under reduced pressure. The residue was chromatograped on silica gel. Elution with 10% ethyl acetate in hexanes gave 46 mg (64%) of the pyrazoline **11**: IR spectrum shows the characteristic N=N stratching band at 1556 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.72 and 4.38 (2H, ABX, J_{AB}= 17.8, J_{AX}=8.7, J_{BX}=6.3 Hz, -N_2CH_2-), 4.06 (2H, s, propargylic CH_2), 3.74 (3H, s, -OMe), 3.45 and 3.34 (2H, ABX, J_{AB}=9.2, J_{AX}=6.9 and J_{BX}=6.4, -OCH_2), 2.60 (1H, m, methine H), 2.18 (2H, t, J=7.0 Hz, propargylic CH_2), 1.52 (3H, s, -CH_3), 1.47-1.35 (4H, m, -$(CH_2)_2$-), 0.88 (3H, t, J=7.3 Hz, -CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 87.6, 76.0, 67.3, 58.9, 58.8, 52.9, 38.2, 30.6, 21.9, 18.3, 15.3, 13.5; Mass (m/z) 267 (M+H), 223, 207, 193, 179, 166, 149, 126, 113 (base peak).

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3. For a discussion of the orbital interactions that control dipolar additions of diazomethane, see: Fleming, I Frontier Molecular Orbitals and Organic Chemistry Reactions; Weily: New York, 1976; pp 148-161.
4. For the examples of [1,3] dipolar cycloaddition with diazomethane, see (1) Martelli, J.; Gree, R. J. Chem. Soc. Chem. Commun **1980**, 8355. (2) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094.
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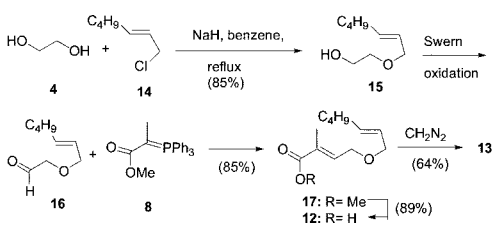
9. The acid **12** was prepared as the following sequence starting from *trans*-2-heptenyl chloride:



10. The spectroscopic data for the compounds **15**, **17**, **12** and **13**. The compound **15**: IR(film) υ 3422, 2925, 1670, 1459, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (2H, dt, J=15.4 and 6.5 Hz, vinyl Hs), 5.53 (1H, dt, J=15.4 and 6.2 Hz, vinyl H), 3.95 (2H, d, J=6.0 Hz, allylic Hs), 3.72 (2H, brt, $HOCH_2$-), 3.52 (2H, brt, $HOCH_2CH_2$-), 2.25-2.20 (3H, brs and brt, -OH and allylic Hs), 1.40-1.29 (4H, m, $CH_3(CH_2)_2$-), 0.87 (3H, t, J=6.9 Hz, -CH_3) ppm. The compound **17**: IR (film) υ 2957, 1722, 1437, 1260, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (1H, t, J=6.0 Hz, vinyl H), 5.70 (1H, dt, J=15.4 and 6.6 Hz, vinyl H), 5.53 (1H, dt, J=15.4 and 6.2 Hz, vinyl H), 4.12 (2H, d, J=6.0 Hz, allylic Hs), 3.92 (2H, d, J=6.2 Hz, allylic Hs), 3.72 (3H, s, -OCH_3), 2.03 (2H, brt, allylic Hs) 1.82 (3H, s, vinyl CH_3), 1.40-1.22 (4H, $CH_3(CH_2)_2$-), 0.87 (3H, t, J=7.0 Hz, -CH_3) ppm. The compound **12**: IR (film) υ 3443, 1649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (1H, t, J=4.5 Hz, vinyl H), 5.70 (1H, dt, J=15.4 and 6.7 Hz, vinyl H), 5.53 (1H, dt, J=15.4 and 6.2 Hz, vinyl H), 4.15 (2H, d, J=5.9 Hz, allylic Hs), 3.93 (2H, d, J=6.3 Hz, allylic Hs), 2.03 (2H, t, J=7.4 Hz, allylic Hs) 1.82 (3H, s, vinyl CH_3), 1.40-1.22 (4H, $CH_3(CH_2)_2$-), 0.87 (3H, t, J=7.0 Hz, -CH_3) ppm. The compound **13**: IR spectrum shows the characteristic N=N stratching band at 1550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.52 (1H, dt, J=15.4 and 7.1 Hz, vinyl H), 5.43 (1H, dt, J=15.4 and 5.2 Hz, vinyl H) 4.70 and 4.34 (2H, ABX, J_{AB}=17.8, J_{AX}=8.7, J_{BX}=6.5 Hz, -N_2CH_2-), 3.82 (2H, d, J=6.2 Hz, allylic CH_2), 3.72 (3H, s, -OMe), 3.33 and 3.21 (2H, ABX, J_{AB}=9.4, J_{AX}=6.9 and J_{BX}=6.3 Hz, -OCH_2), 2.58 (1H, m, methine H), 2.33 (2H, m, allylic CH_2), 1.47 (3H, s, -CH_3), 1.40-1.20 (4H, m, -$(CH_2)_2$-), 0.85 (3H, t, J=7.3 Hz, -CH_3) ppm.
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