Synthesis of Quinazoline Derivatives through Anionic Cycloaddition Reactions of Methyl 2,4-Dimethoxy-6-methyl-5-pyrimidinecarboxylate with Acetylenes and Olefins

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The anionic cycloaddition of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate has been investigated. The lithium salt of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate, generated by deprotonation with lithium diisopropylamide in ether at −70°, reacted smoothly with electron deficient acetylenes and olefins to give quinazoline derivatives in a single step.

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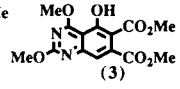
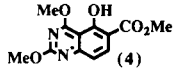
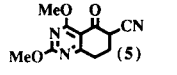
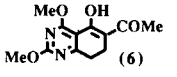
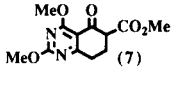
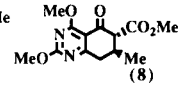
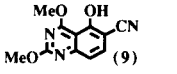
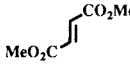
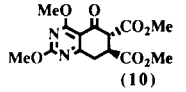
A number of reports has appeared on anionic cycloaddition reactions using a benzylic carbanion [2-6], and these reactions provide novel methods for the synthesis of certain natural products such as pyranonaphthoquinone and anthracyclinone antibiotics. However, little attention has been given to analogous reactions of heteroaromatics [7]. We have recently communicated that the lithium salt of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate (**2**) can reacts as a 1,4-dipole synthon with carbon-carbon multiple bonds having an electron withdrawing group to afford quinazoline compounds in a single step [8]. This paper describes a full account of this work including the reaction mechanism.

The starting ester, methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate (**1**), was prepared from the corresponding acid [9] by methylation using ethereal diazomethane. Treatment of **1** in anhydrous ether with 1.2 equivalents of lithium diisopropylamide (LDA) at −70° for 10 minutes gave the lithium derivative **2**, which was quenched with dimethyl acetylenedicarboxylate to afford the cycloadduct **3** in 38% yield with the recovery of the starting material (60%) (Scheme 1). In a similar fashion, the lithium salt **2** reacted with various types of carbon-carbon multiple bonds to give the quinazoline compounds **4-10** in moderate yields. These results were summarized in the Table.

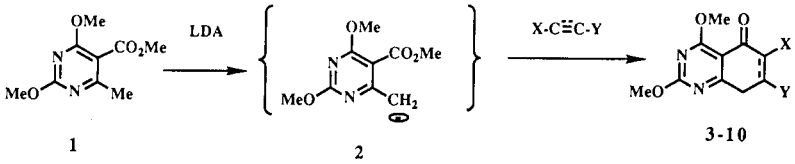
The attractive feature of these cycloadditions is that the quinazoline derivatives were obtained regioselectively in such a way the carbanion **2** generally reacted at the more positive site of the carbon-carbon multiple bonds (Runs

Table

Cycloaddition of 2 with Some Acetylenes and Olefins

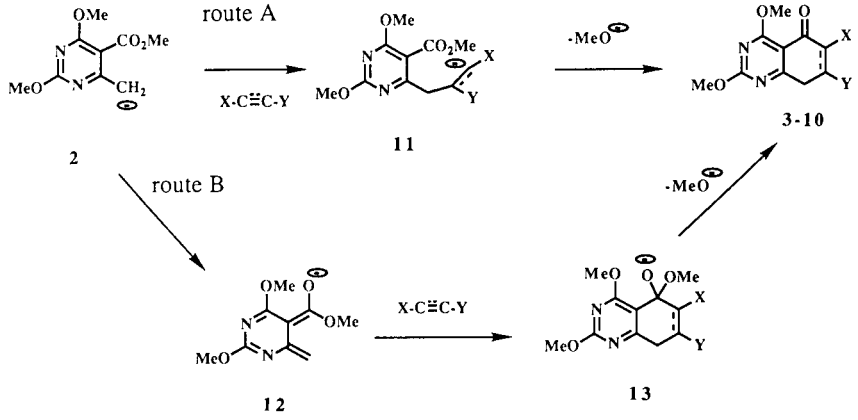
Runs	Acetylenes or Olefins	Product	Yield (%)	Recovery (%)
1	$MeO_2C{\cdot}C{\equiv}C{\cdot}CO_2Me$	 (3)	38	60
2	$HC{\equiv}C{-}CO_2Me$	 (4)	24	49
3	$H_2C{=}CH{-}CN$	 (5)	29	48
4	$H_2C{=}CH{-}COMe$	 (6)	30	20
5	$H_2C{=}CH{-}CO_2Me$	 (7)	55	38
6	$Me{-}CH{=}CH{-}CO_2Me$	 (8)	47	32
7	$MeO{-}CH{=}CH{-}CO_2Me$	(4)	37	24
8	$MeO{-}CH{=}CH{-}CN$	 (9)	28	42
9		 (10)	14	56
10		(10)	12	58

Scheme 1



1 2 3-10

Scheme 2



2-8). The structure of the products were determined on the basis of elemental analysis and spectral data. The cycloadduct **6** from methyl vinyl ketone was found to exist mainly in the enolic form, which hydroxy signal was shown at δ = 16.55 in its ^{1}H nuclear magnetic resonance spectrum. In contrast the ^{1}H nmr spectra of the nitrile and methoxycarbonyl derivatives **5**, **7**, **8**, and **10**, obtained from the reaction with acrylonitrile, methyl acrylate, methyl crotonate, dimethyl fumarate, and dimethyl maleate, showed that the products were in the keto form. The stereochemistry of **8** and **10** were assigned as *trans* from the coupling constant between the C-6 and C-7 protons (12 Hz for **8**, 10 Hz for **10**). In the reactions of methyl 3-methoxypropenate and 3-methoxypropennitrile, the aromatized products **4** and **9** were obtained *via* the elimination of methanol from the initially formed cycloadducts.

There are two possible routes for the formation of a cycloadduct from the lithium salt **2**, i) the Michael addition of the carbanion with acetylene or olefin followed by spontaneous cyclization of intermediate **11** (route A) or ii) [4+2] cycloaddition of the dienol isomer **12** from **2** to the acetylene or olefin to give **13** and subsequent elimination of methoxide (route B) as shown in the Scheme 2.

Route A has been observed in the cycloaddition of metallated *o*-toluate [2], *o*-toluamide [3], phthalide [4] or homophthalate [5] with Michael acceptors. Route B has been observed in the base induced cycloaddition of homophthalic anhydride [6] with active dienophiles. Although we could not obtain definite evidence, route A seems to be most favorable for the anionic cycloaddition of **1** to the acetylenes and olefins from the fact that the same product was obtained in the reaction of **1** with dimethyl fumarate and dimethyl maleate (Runs 9 and 10) [10]. This speculation was supported by Senda's report, in which they obtained different products in the photocycloaddition of 5-carbonyl substituted 1,3,6-trimethyluracils with dimethyl fumarate and dimethyl maleate under basic conditions [11].

EXPERIMENTAL

Measurements.

All melting points were determined by using a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270 spectrometer. Proton magnetic resonance spectra were determined on a JEOL JNM-MH-100 instrument using tetramethylsilane as the internal standard. Mass spectra were obtained with a JEOL JMS-100 instrument with a direct inlet system.

Methyl 2,4-Dimethoxy-6-methyl-5-pyrimidinecarboxylate (**1**).

This was prepared from 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylic acid (5 g, 25 mmoles) [9] in the usual manner using ethereal diazomethane in 92% yield (4.9 g), mp 76-77° (petroleum ether); ir (chloroform): 1725, 1580 cm^{-1}; ^{1}H nmr (deuteriochloroform): 2.44 (3H, s, Me), 3.87 (3H, s, OMe), 4.01 (6H, s, OMe x 2) ppm; ms: m/z 212 (M$^+$).

Anal. Calcd. for $C_9H_{12}O_4N_2$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.88; H, 5.29; N, 13.34.

General Procedure for the Reaction of **1** with Acetylenes and Olefins.

A solution of *n*-butyllithium (1.6*N*, 2.6 ml, 4.2 mmoles) and diisopropylamine (590 mg, 4.2 mmoles) in dry ether (20 ml) was stirred under a nitrogen atmosphere at 0° for 15 minutes. The resulting solution was cooled at −70°, followed by addition of 30 ml of an ether solution of **1** (5 mmoles), followed by stirring for 20 minutes. The appropriate acetylene or olefin (5 mmoles) dissolved in ether (10 ml) was added dropwise over a 5 minute period. The reaction mixture was warmed slowly to room temperature, and then quenched by the addition of a saturated aqueous ammonium chloride solution (30 ml). The organic layer was separated and the aqueous layer was extracted with ether (40 ml x 3). The combined organic layers were washed with aqueous sodium chloride (80 ml) and then dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (chloroform/ethyl acetate, 9/1) to afford the product.

Dimethyl 2,4-Dimethoxy-5-hydroxyquinazoline-6,7-dicarboxylate (**3**).

This was prepared from **1** (210 mg, 1.0 mmole) and dimethyl

acetylenedicarboxylate (160 mg, 1.1 mmoles) in 38% yield (115 mg), mp 152-154° (methanol); ir (chloroform): 3530, 1740, 1675, 1630, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 4.08 (3H, s, OMe), 4.21 (3H, s, OMe), 7.32 (1H, s, C8-H), 11.55 (1H, s, OH) ppm; ms: m/z 322 (M^+).

Anal. Calcd. for $C_{14}H_{14}N_2O_7$: C, 52.17; H, 4.38; N, 8.69. Found: C, 52.22; H, 4.55; N, 8.58.

Methyl 2,4-Dimethoxy-5-hydroxyquinazoline-6-carboxylate (**4**).

i) This was prepared from **1** (425 mg, 2.0 mmoles) and methyl propiolate (170 mg, 2.1 mmoles) in 24% yield (128 mg), mp 157-159° (methanol); ir (chloroform): 3650, 1670, 1635, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 3.98 (3H, s, OMe), 4.07 (3H, s, OMe), 4.19 (3H, s, OMe), 7.21 (1H, d, J = 9 Hz, C8-H), 8.13 (1H, d, J = 9 Hz, C7-H), 11.38 (1H, s, OH), ppm; ms: m/z 264 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.58; N, 10.60. Found: C, 54.47; H, 4.55; N, 10.58.

ii) This was prepared from **1** (400 mg, 1.98 mmoles) and methyl 3-methoxypropenate (250 mg, 2.1 mmoles) in 37% yield (185 mg). This was identical with the sample obtained in i).

6-Cyano-5,6,7,8-tetrahydro-2,4-dimethoxy-5-oxoquinazoline (**5**).

This was prepared from **1** (300 mg, 1.4 mmoles) and acrylonitile (100 mg, 1.9 mmoles) in 29% yield (97 mg), mp 177-180° (methanol); ir (chloroform): 2260, 1700, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 2.3-2.6 (2H, m, CH_2), 3.0-3.2 (2H, m, CH_2), 3.6-3.9 (1H, m, CH), 4.02 (3H, s, OMe), 4.08 (3H, s, OMe) ppm; ms: m/z 233 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.41; H, 4.55; N, 18.21.

6-Acetyl-5,6,7,8-tetrahydro-2,4-dimethoxy-5-oxoquinazoline (**6**).

This was prepared from **1** (400 mg, 1.98 mmoles) and methyl vinyl ketone (160 mg, 2.1 mmoles) in 30% yield (142 mg), mp 127-131° (dichloromethane-petroleum ether); ir (chloroform): 3550, 1715, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 2.15 (3H, s, COMe), 2.61 (2H, t, J = 7 Hz, CH_2), 2.88 (2H, t, J = 7 Hz, CH_2), 4.03 (3H, s, OMe), 4.10 (3H, s, OMe), 16.31 (1H, s, OH) ppm; ms: m/z 250 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.69; H, 5.55; N, 11.42.

Methyl 5,6,7,8-Tetrahydro-2,4-dimethoxy-5-oxoquinazoline-6-carboxylate (**7**).

This was prepared from **1** (300 mg, 1.4 mmoles) and methyl acrylate (140 mg, 1.8 mmoles) in 55% yield (207 mg), mp 102-104° (dichloromethane-petroleum ether); ir (chloroform): 1740, 1690, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 2.2-2.5 (2H, m, CH_2), 2.8-3.1 (2H, m, CH_2), 3.53 (1H, dd, J = 7 and 5.5 Hz, CH), 3.71 (3H, s, OMe), 3.99 (3H, s, OMe), 4.04 (3H, s, OMe) ppm; ms: m/z 266 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.27; H, 5.55; N, 10.58.

Methyl 5,6,7,8-Tetrahydro-2,4-dimethoxy-6-methyl-5-oxoquinazoline-6-carboxylate (**8**).

This was prepared from **1** (300 mg, 1.4 mmoles) and methyl crotonate (150 mg, 1.5 mmoles) in 47% yield (185 mg), mp 102-105° (dichloromethane-petroleum ether); ir (chloroform): 1745, 1685, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 1.14 (3H, d, J = 6 Hz, Me), 2.5-2.7 (2H, m, C7-H), 2.69 (1H, dd, J = 22, 11 Hz, C8-H), 3.11 (1H, dd, J = 22, 9 Hz, C8-H), 3.29 (1H, d, J = 12 Hz, C6-H), 3.79 (3H, s, OMe), 4.05 (3H, s, OMe), 4.09 (3H, s, OMe) ppm; ms: m/z 280 (M^+).

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 10.00. Found: C, 55.63; H, 5.49; N, 10.19.

6-Cyano-2,4-dimethoxy-5-hydroxyquinazoline (**9**).

This was prepared from **1** (400 mg, 1.98 mmoles) and 3-methoxypropenenitrile (200 mg, 2.4 mmoles) in 28% yield (124 mg), mp 199-202° (methanol); ir (nujol): 3480, 2260, 1575 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): 3.98 (3H, s, OMe), 4.16 (3H, s, OMe), 7.14 (1H, d, J = 8 Hz, C8-H), 7.88 (1H, d, J = 8 Hz, C7-H), OH is absence; ms: m/z 231 (M^+).

Anal. Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.22; H, 4.02; N, 18.21.

Dimethyl 5,6,7,8-Tetrahydro-2,4-dimethoxy-5-oxoquinazolin-5,6-dicarboxylate (**10**).

i) This was prepared from **1** (300 mg, 1.4 mmoles) and dimethyl fumarate (220 mg, 1.5 mmoles) in 14% yield (64 mg), mp 128-130° (ether); ir (chloroform): 1740, 1690, 1595, 1555 cm^{-1}; ^1H nmr (deuteriochloroform): 3.14 (1H, dd, J = 18, 10 Hz, C8-H), 3.37 (1H, dd, J = 18, 5 Hz, C8-H), 3.59 (1H, dt, J = 10, 5 Hz, C7-H), 3.74 (3H, s, OMe), 3.80 (3H, s, OMe), 3.89 (1H, d, J = 10 Hz, C6-H), 4.06 (3H, s, OMe), 4.09 (3H, s, OMe) ppm; ms: m/z 324 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.91; H, 4.99; N, 8.71.

ii) This was prepared from **1** (300 mg, 1.4 mmoles) and dimethyl maleate (220 mg, 1.5 mmoles) in 12% yield (53 mg). This was identical with an authentic sample obtained in i).

REFERENCES AND NOTES

[1] Present address: Kobe Women's College of Pharmacy, 4-19-1, Motoyamakita-machi, Higashinada-ku, Kobe 658, Japan.

[2] *o*-Toluate: F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, **43**, 178 (1978); G. E. Evans, F. J. Leeper, J. A. Murphy and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 205 (1979); E. J. Leeper and J. Staunton, *ibid.*, 206 (1979); J. H. Dodd and S. M. Weinreb, *Tetrahedron Letters*, 3593 (1979); J. H. Dodd, R. S. Garigipati and S. M. Weinreb, *J. Org. Chem.*, **47**, 4045 (1982); J. H. Dodd, J. E. Starrett, Jr. and S. M. Weinreb, J. Am. Chem. Soc., **106**, 1811 (1984).

[3] *o*-Toluamide: M. Date, M. Watanabe and S. Furukawa, *Chem. Pharm. Bull.*, **38**, 902 (1990); R. D. Clark and Jahangir, *J. Org. Chem.*, **52**, 5378 (1987); *idem., ibid.*, **54**, 1174 (1989); *idem., ibid.*, **53**, 2378 (1988); Jahangir, L. E. Fisher, R. D. Clark and J. M. Muchowski, *ibid.*, **54**, 2992 (1989).

[4] Phthalide: G. A. Kraus and H. Sugimoto, *Tetrahedron Letters*, 2263 (1978); F. M. Hauser and S. Prasanna, *J. Org. Chem.*, **44**, 2596 (1979); *idem., ibid.*, **47**, 383 (1982); *idem., J. Am. Chem. Soc.*, **103**, 6378 (1981); F. M. Hauser, S. Prasanna and D. M. Combs, *J. Org. Chem.*, **48**, 1328 (1983); N. J. P. Broom and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, 162 (1978); *idem., J. Chem. Soc., Perkin Trans. I*, 465 (1981); R. A. Russell and R. N. Warrener, *J. Chem. Soc., Chem. Commun.*, 108 (1981); F. M. Hauser and D. Mal, *J. Am. Chem. Soc.*, **105**, 5688 (1983); K. Tatsuta, K. Akimoto, M. Annaka, Y. Ohno and M. Kinoshita, *Bull. Chem. Soc. Japan*, **58**, 1699 (1985); J. N. Freslos and J. S. Swenton, *J. Chem. Soc., Chem. Commun.*, 658 (1985).

[5] Homophthalate: W. Eisenmuth, H. B. Renfroe and H. Schmidt, *Helv. Chim. Acta*, **48**, 375 (1965); B. L. Chenard, M. G. Dolson, A. D. Sercel and S. Swenton, *J. Org. Chem.*, **49**, 318 (1984).

[6] Homophthalic Anhydride: Y. Tamura, A. Wada, M. Sasho, K.

Fukunaga, H. Maeda and Y. Kita, *J. Org. Chem.*, **47**, 4376 (1982); Y. Tamura, M. Sasho, S. Akai, A. Wada and Y. Kita, *Tetrahedron*, **40**, 4539 (1984); Y. Tamura, M. Sasho, K. Nakajima, T. Tsugoshi and Y. Kita, *J. Org. Chem.*, **49**, 473 (1984); Y. Tamura, M. Sasho, S. Akai, H. Kishimoto, J. Sekihachi and Y. Kita, *Tetrahedron Letters*, **27**, 195 (1986); *idem.*, *Chem. Pharm. Bull.*, **35**, 1405 (1987).

[7] Y. Tamura, S. Mohri, H. Maeda, T. Tsugoshi, M. Sasho and Y. Kita, *Tetrahedron Letters*, **25**, 309 (1984); Y. Kita, S. Mohri, T. Tsugoshi, H. Maeda and Y. Tamura, *Chem. Pharm. Bull.*, **33**, 4723 (1985); Y. Tamura, M. Kirihara, M. Sasho, S. Akai, J. Sekihachi, R. Okunaka and Y. Kita, *J. Chem. Soc., Chem. Commun.*, 1474 (1987).

[8] A. Wada, H. Yamamoto and S. Kanatomo, *Heterocycles*, **27**, 1345 (1988).

[9] S. Kanatomo, A. Wada, M. Yomei, T. Hase, S. Nagai, S. Fukuda, M. Tanaka and T. Sasaki, *Chem. Pharm. Bull.*, **36**, 2042 (1988).

[10] Also, we could isolate the Michael adducts in the reaction of **1** with some α,β-unsaturated ketones, and these results will be published elsewhere.

[11] S. Senda, T. Asano, I. Sugiyama and K. Hirota, *Tetrahedron Letters*, 531 (1980).