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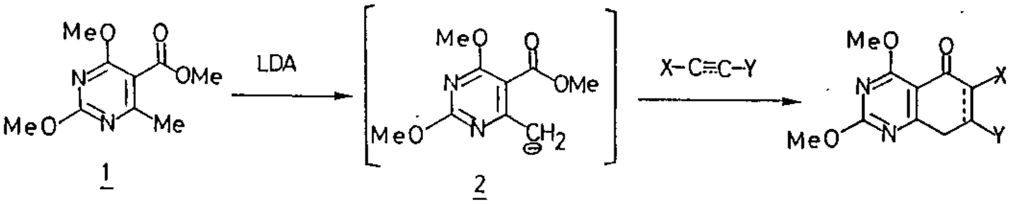
ANIONIC CYCLOADDITION OF METHYL 2,4-DIMETHOXY-6-METHYL-5-PYRIMIDINECARBOXYLATE WITH ACETYLENES AND OLEFINS

Akimori Wada,* Hiromi Yamamoto, and Shōichi Kanatomo
School of Pharmacy, Hokuriku University, Ho-3, Kanagawa-machi,
Kanazawa 920-11, Japan

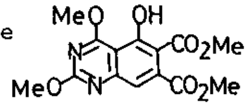
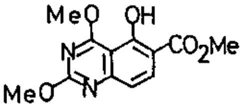
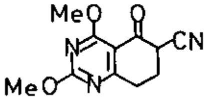
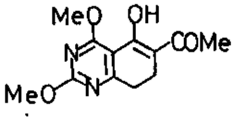
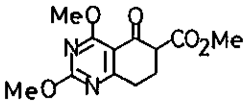
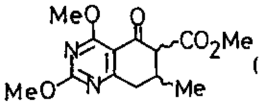
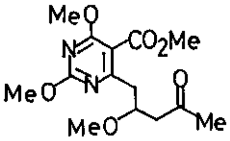
Abstract ——The lithium salt of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate reacts with electron deficient acetylenes and olefins to afford quinazoline derivatives via anionic cycloaddition in considerable yields.

Although the ortho-toluate anion reacts readily with Michael acceptors to afford cycloadducts[1] and has been profitably used for the synthetic approach to certain natural products,[2,3] there has been no report dealing with analogous reactions of heteroaromatics. We recently found that lithium carbanion (2) derived from methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate (1) reacted with C=C and C≡C bonds having an electron withdrawing group, where 1 acted as a 1,4-dipole synton in the cycloaddition reaction. The present paper describes a simple and direct route to quinazoline derivatives with regioselectivity.



The carbanion (2) was generated by the reaction of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate (1)[4] with lithium diisopropylamide (LDA) in ether at -70°C under nitrogen, and reacted with 1.1 equivalent of acetylenes or olefins (3-8) to afford the corresponding cycloadducts (9-14). Cycloaddition occurred regioselectively in such a way that the carbanion (2) generally reacted at the unsubstituted carbon site of the carbon-carbon multipul

Table. Cycloaddition Reactions of 2 with Some Acetylenes and Olefins

Run	Acetylene or Olefin	Product[a]	Yield[b] (%)	Recovery[b] (%)	M.p. (°C)[c] (Solvent)
1	$MeO_2C-C{\equiv}C-CO_2Me$ (3)	 (9)	38	60	152-154 (MeOH)
2	$HC{\equiv}C-CO_2Me$ (4)	 (10)	24	49	157-159 (MeOH)
3	$H_2C=CH-CN$ (5)	 (11)	29	48	177-180 (MeOH)
4	$H_2C=CH-COMe$ (6)	 (12)	30	20	127-131 (CH_2Cl_2-pet.ether)
5	$H_2C=CH-CO_2Me$ (7)	 (13)	55	38	102-104 (CH_2Cl_2-pet.ether)
6	$Me-CH=CH-CO_2Me$ (8)	 (14)[d]	47	32	102-105 (CH_2Cl_2-pet.ether)
7	$MeO-CH=CH-COMe$ (18)	 (19)	25	44	95-96 (MeOH)

a) All spectroscopic data (nmr, ir, and mass spectra) are in good agreement with the proposed structures.

b) Isolated yields are based on 1.

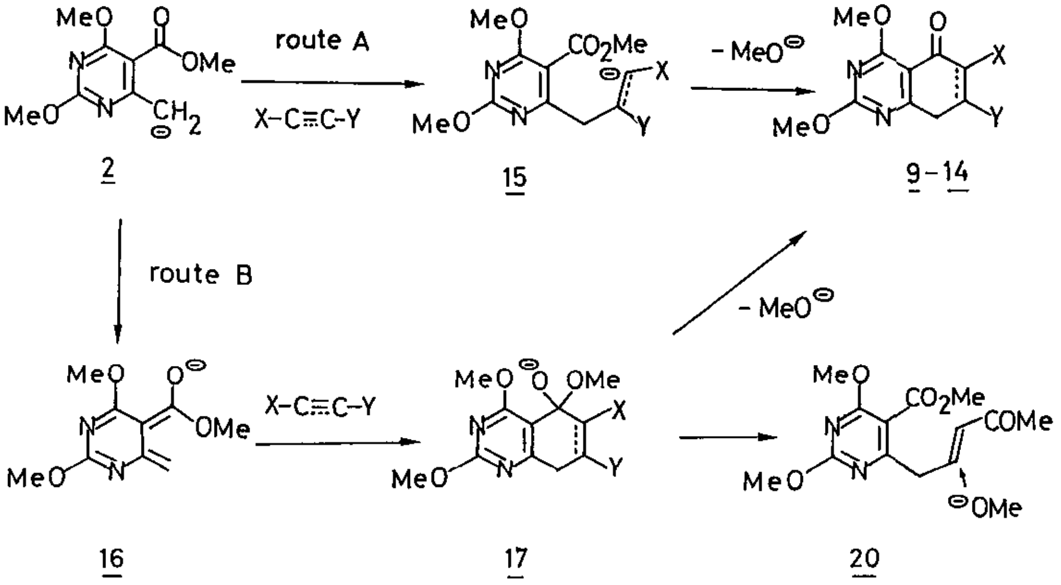
c) The melting points are not corrected.

d) The stereochemistry could not be confirmed .

bond (Run 2-5).[5] The structures of the products were characterized by ir, ^{1}H-nmr and mass spectral data. The yields are listed in the Table.

There are two possible routes for the formation of a cycloadduct from the lithium salt (2), the Michael addition of carbanion with acetylene or olefin followed by spontaneous cyclization of intermediate (15) (route A) or [4+2] cycloaddition of the dienol isomer (16) from 2 to the acetylene or olefin to give 17 and subsequent elimination of methoxide (route B)[6] as shown in the Scheme. Although, in the reaction of 2 with 4-methoxy-3-buten-2-one (18), only a Michael adduct (19) was obtained in 25% yield, it was also understandable that 19 was produced from the intermediate (20) through route B.

As we could not obtaine definite evidence, further investigation is currently in progress.



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3. J.H. Dodd and S.M. Weinreb, *Tetrahedron Lett.*, 1979, 3593; J.H. Dodd, R.S. Garigipati, and S.M. Weinreb, *J. Org. Chem.*, 1982, **47**, 4045.
4. This compound was prepared from 5-bromo-2,4-dimethoxy-6-methylpyrimidine by halogen lithium exchange followed by the treatment of carbon dioxide, and esterification with ethereal diazomethane: mp 76-77 °C (pet.ether); ν max ($CHCl_3$) 1725, 1580; δ ($CDCl_3$) 4.01 (s, 6H, OMeX2), 3.87 (s, 3H, OMe), 2.44 (s, 3H, Me).
5. Similar cycloaddition of benzylic carbanion has already been reported, see the following examples. (a) Phthalide: G.A. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 1978, 2263; F.M. Hauser and S. Prasanna, *J. Org. Chem.*, 1979, **44**, 2596; idem, *ibid.*, 1982, **47**, 383; idem, *J. Am. Chem. Soc.*, 1981, **103**, 6378; F.M. Hauser, S. Prasanna, and D.M. Combs, *J. Org. Chem.*, 1983, **48**, 1328; N.J.P. Broom and P.G. Sammes, *J. Chem. Soc. Chem. Commun.*, 1978, 162; idem, *J. Chem. Soc. Perkin I*, 1981, 465; R.A. Russell and R.N. Warrener, *J. Chem. Soc., Chem. Commun.*, 1981, 108. (b) Homophthalate: W. Eisenmuth, H.B. Renfroe, and H. Schmidt, *Helv. Chim. Acta*, 1965, **48**, 375; B.L. Chenard, M.G. Dolson, A.D. Sercel, and S. Swenton, *J. Org. Chem.*, 1984, **49**, 318. (c) Homophthalic Anhydride: Y. Tamura, A. Wada, M. Sasho, K. Fukunaga, H. Maeda, and Y. Kita, *J. Org. Chem.*, 1982, **47**, 4376; Y. Tamura, M. Sasho, S. Akai, A. Wada, and Y. Kita, *Tetrahedron*, 1984, **40**, 4539; Y. Tamura, M. Sasho, K. Nakajima, T. Tsugoshi, and Y. Kita, *J. Org. Chem.*, 1984, **49**, 473; Y. Tamura, M. Sasho, S. Akai, H. Kishimoto, J. Sekihachi, and Y. Kita, *Tetrahedron Lett.*, 1986, **27**, 195.
6. Senda et al. proposed the [4+2] cycloaddition mechanism in the reaction of 5-carbonyl-substituted 1,3,6-trimethyluracil with electron deficient dienophiles; S. Senda, T. Asao, I. Sugiyama, and K. Hirota, *Tetrahedron Lett.*, 1980, 531.

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