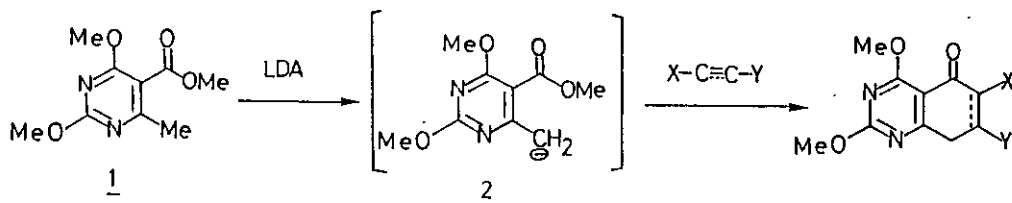


## ANIONIC CYCLOADDITION OF METHYL 2,4-DIMETHOXY-6-METHYL-5-PYRIMIDINECARBOXYLATE WITH ACETYLENES AND OLEFINS

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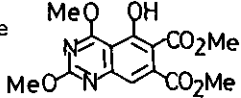
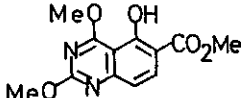
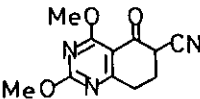
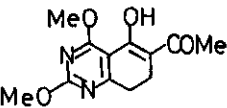
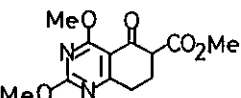
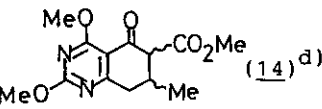
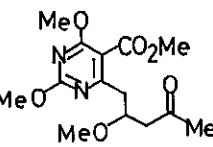
**Abstract** — The lithium salt of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate reacts with electron deficient acetylenes and olefins to afford quinazoline derivatives via anionic cycloaddition in considerable yields.

Although the ortho-toluate anion reacts readily with Michael acceptors to afford cycloadducts<sup>1</sup> and has been profitably used for the synthetic approach to certain natural products,<sup>2,3</sup> 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 synthon 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)<sup>4</sup> 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 <sup>a)</sup>	Yield <sup>b)</sup> (%)	Recovery <sup>b)</sup> (%)	M.p. (°C) <sup>c)</sup> (Solvent)
1	MeO <sub>2</sub> C-C≡C-CO <sub>2</sub> Me (3)	 (9)	38	60	152-154 (MeOH)
2	HC≡C-CO <sub>2</sub> Me (4)	 (10)	24	49	157-159 (MeOH)
3	H <sub>2</sub> C=CH-CN (5)	 (11)	29	48	177-180 (MeOH)
4	H <sub>2</sub> C=CH-COMe (6)	 (12)	30	20	127-131 (CH <sub>2</sub> Cl <sub>2</sub> -pet.ether)
5	H <sub>2</sub> C=CH-CO <sub>2</sub> Me (7)	 (13)	55	38	102-104 (CH <sub>2</sub> Cl <sub>2</sub> -pet.ether)
6	Me-CH=CH-CO <sub>2</sub> Me (8)	 (14) <sup>d)</sup>	47	32	102-105 (CH <sub>2</sub> Cl <sub>2</sub> -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.

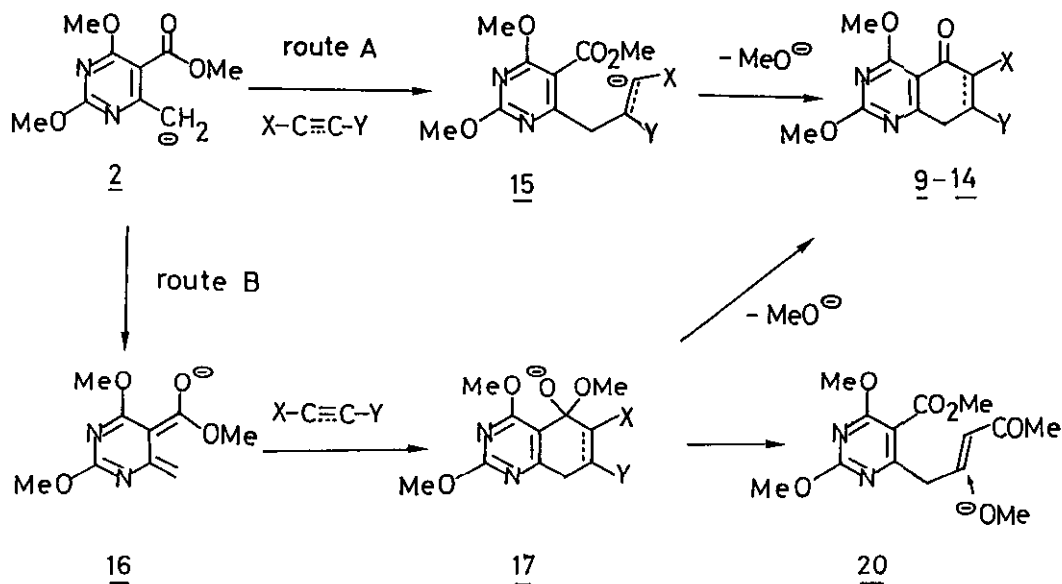
b) Isolated yields are based on **1**.

c) The melting points are not corrected.

d) The stereochemistry could not be confirmed.

bond (Run 2-5).<sup>5</sup> The structures of the products were characterized by ir, <sup>1</sup>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)<sup>6</sup> 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 obtain definite evidence, further investigation is currently in progress.



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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);  $\nu$  max (CHCl<sub>3</sub>) 1725, 1580;  $\delta$  (CDCl<sub>3</sub>) 4.01 (s, 6H, OMe<sub>2</sub>), 3.87 (s, 3H, OMe), 2.44 (s, 3H, Me).
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