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AN EFFICIENT MULTICOMPONENT REACTION INVOLVING THE INTERCEPTION OF THE ZWITTERIONIC INTERMEDIATE BETWEEN DMAD AND ISOCYANIDES WITH SOME ACTIVE METHYLENE COMPOUNDS[f]

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Abstract-The 1:1 zwitterionic intermediate generated from dimethyl acetylenedicarboxylate and isocyanide is intercepted with 2-hydroxy-1,4-naphthoquinone, 4-hydroxycoumarin, 4-hydroxy-1-methylquinolinone, 4-hydroxy-6-methylpyrone, and 1-naphthol in one-pot to give novel pyran annulated heterocyclic systems in good yields.

Multicomponent reactions (MCRs) by virtue of their many attributes, especially, facility of execution and high efficiency, have invoked enormous interest in the last two decades.[1] MCRs, particularly the Ugi, Passerini and related reactions provide many opportunities to discover new reactions and basic structures.[2] Extensive efforts are now being made in this area, especially from the vantage point of combinatorial chemistry.[3]

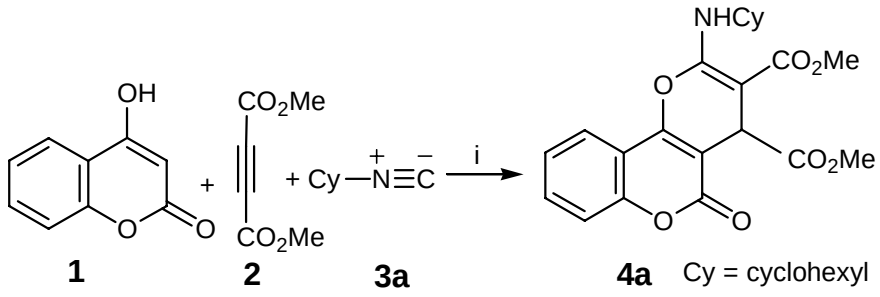
Previously we have designed some facile three component reactions for the construction of heterocyclic systems such as aminofurans,[4] iminolactones[5] and aminopyrroles.[6] The strategy adopted is mainly based on the formation of 1:1 zwitterionic species from dimethyl acetylenedicarboxylate (DMAD) and

[f] This paper is dedicated to Professor Albert Meyers in appreciation of his original contributions in the area of heterocyclic chemistry on the occasion of his 70th birthday.

isocyanide[7] and its interception with an electrophilic component. We surmised that trapping of the zwitterionic intermediate with various active methylene compounds would lead to interesting heterocycles, thereby extending the scope of the reaction. Except for an isolated report on such interception using *N, N*-dimethylbarbituric acid leading to 4*H*-pyrano[3,2-*d*]pyrimidine derivatives,[8] there has been no efforts on this line.

Against the background presented above, we investigated the interception of 1:1 zwitterionic intermediate with a variety of cyclic active methylene compounds with the perception that such a reaction sequence would lead to novel pyran annulated heterocycles, thus constituting a novel multiple component reaction. The preliminary results of our investigation are presented in this paper.

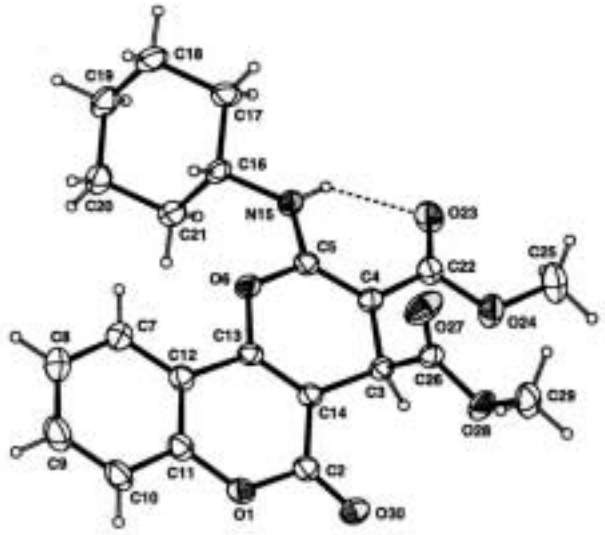
Our studies were initiated by treating 4-hydroxycoumarin with dimethyl acetylenedicarboxylate and stoichiometric amount of cyclohexyl isocyanide in refluxing benzene; the reaction afforded a colorless crystalline solid in 68% yield characterized as **4a** (Scheme 1). [10]



i = Benzene, Ar, 80 °C, 6 h, 68%

Scheme 1

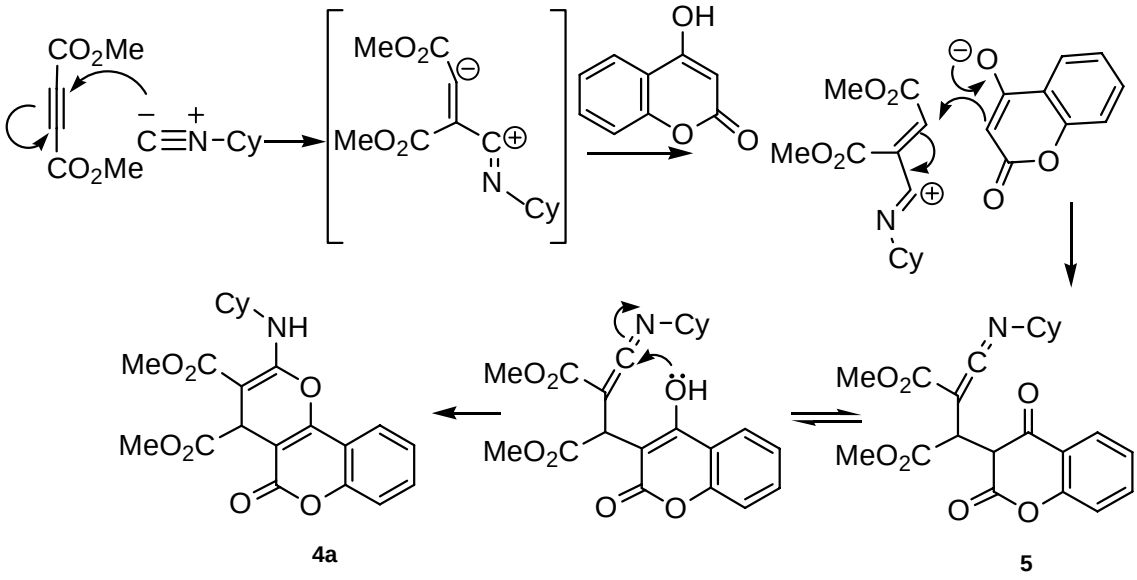
The IR spectrum of product (**4a)** showed methoxycarbonyl absorptions at 1726 and 1693 cm^{-1} and the -NH absorption at 3271 cm^{-1}. In the ^{1}H NMR spectrum, the characteristic methoxy protons appeared as singlets at δ 3.74 and 3.71. The signal at δ 4.70 is attributed to the diallylic methine proton α to the ester group. The amine hydrogen atom resonated at δ 8.73 (exchangeable by D_2O) indicating extensive intramolecular hydrogen bond formation with the vicinal ester carbonyl group. In the ^{13}C NMR spectrum, the ester carbonyls were observed at δ 172.82 and 169.10. Finally the assigned structure was confirmed unambiguously by single crystal X-Ray analysis (Figure).



Single crystal X-Ray structure for **4a**

Figure

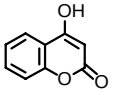
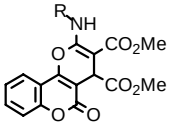
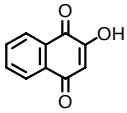
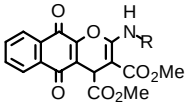
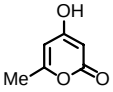
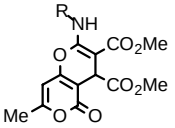
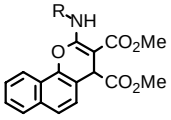
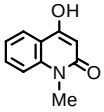
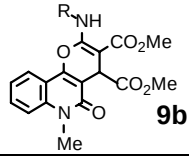
Mechanistically, the reaction may be rationalized as shown in Scheme 2. Protonation of the 1:1 zwitterionic intermediate by the hydroxycoumarin followed by the quenching of the cationic center by the enolate can conceivably generate the ketenimine (**5)**. Cyclization of the latter and subsequent isomerization culminated in the formation of **4a**.



Scheme 2

Similarly, the reaction of 2-hydroxy-1,4-naphthoquinone, 4-hydroxy-6-methyl pyrone and α-naphthol afforded the corresponding condensation products in good yields. The reaction can easily be extended to employ *tert*-butyl isocyanide (**3b**)[11] as the nucleophile without compromising chemical efficiency. The results are presented in Table.

Table: Trapping of isocyanide-DMAD zwitterion with various cyclic active methylene compounds.

No.	Substrate	Product	R = Cy time (h)	R = Cy Yield(%)	R = *t*-Bu time (h)	R = *t*-Bu Yield(%)
1		 **4a-b**	6	68	5	93
2		 **6a-b**	7	63	7	83
3		 **7a-b**	4	80	2.5	98
4		 **8a-b**	5	49	3	65
5		 **9b**	-	-	1.5	98

Where Cy = cyclohexyl.

In conclusion, we have found that the one-pot reaction of isocyanides and DMAD with various active methylene compounds offers a facile synthesis of polycyclic pyran derivatives.[12]

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10. Representative experimental procedure and spectral data for dimethyl 5-*tert*-butylamino-5,10-dioxo-5,10-dihydro-2*H*-benzo[*g*]chromene-3,4-dicarboxylate (**6b)** (No. 2, Table). A mixture of 2-hydroxy-1,4-naphthoquinone (174 mg, 1 mmol) and DMAD (156 mg, 1.1 mmol) in anhydrous benzene at 80 °C was purged with argon for 5 min, followed by the addition of *t*-butyl isocyanide (92 mg, 1.1 mmol). The reaction mixture was refluxed for 7 h and the residue obtained after removal of the solvent was dissolved in CH_2Cl_2-hexane mixture (3+4 mL) and the solution was kept in a refrigerator overnight and the crystallized product was separated and washed with hexane to give a wine red crystalline solid (330 mg, 83%). mp 152-153 °C (recrystallized from CH_2Cl_2-hexane).IR (KBr) ν_{max}: 3231, 2962, 1728, 1667, 1600, 1445, 1364, 1276, 1202 cm^{-1}.^{1}H NMR ($CDCl_3$ + CCl_4 = 7:3): δ 8.75 (s, 1H), 8.11-8.14 (m, 2H), 7.73-7.80 (m, 2H), 4.74 (s, 1H), 3.50 (s, 3H), 3.43 (s, 3H), 1.52 (m, 10H). ^{13}C NMR $CDCl_3$ + CCl_4 = 7:3):δ 182.49, 177.01, 172.04, 169.14, 159.96, 149.65, 134.40, 133.78, 131.55, 130.66, 126.73, 126.48, 122.03, 71.79, 53.32, 52.55, 50.96, 35.46, 30.32. Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.50; H, 5.12; N, 3.21.
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