Synthesis of Trisubstituted-4H-Pyrans *via* Unexpected Cycloaddition of Aldehydes with Acetylenic Ketones Mediated by DMAP and 2,4-Pentanedione

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Abstract: A cycloaddition of aldehydes and acetylenic ketones mediated by 4-dimethylaminopyridine and 2,4-pentanedione is reported. The method supplies a facile way to synthesize 3,4,5-trisubstituted-4H-pyrans in moderate to good yields under mild conditions.

Keywords: Cycloaddition, acetylenic ketones, aldehydes, 4H-pyran, DMAP, 2,4-pentanedione.

INTRODUCTION

Heterocycles are of great importance due to their potential in the discovery of new biologically active compounds [1,2]. The development of an efficient hetero-cyclization using metal-free catalyst has been drawing much attention over the past decades [3-5]. Recently, reactions based on nucleophilic catalysis *via* conjugate addition of N- and P-nucleophiles have proven to be useful for the development of new annulation reactions providing various heterocycles [6-17]. Despite the reaction of aldehydes with acetylides has been reported [18,19], there exist no reports on the synthesis of 4H-pyrans through Zwitterionic species with aldehydes [20]. Herein, we wish to report a hetero-cyclization of aldehydes with acetylenic ketones mediated by 4-dimethylaminopyridine (DMAP) and 2,4-pentanedione.

Recently, we have described a three-component reaction of aldehydes with acetylenic ketones and 1,3-dicarbonyl moieties, catalyzed by triphenylphosphine to synthesize multi-carbonyl compounds (Scheme **1**) [21]. When DMAP, in place of Ph_3P, was tested as a catalyst, a new cycloaddition reaction had happened. For example, reaction of 3-butyn-2-one with 4-nitrobenzaldehyde and 2,4-pentanedione in the presence of DMAP gave a new product. The structure of the product was assigned as 3,4,5-trisubstitued-4H-pyrane **4a** on the basis of spectroscopic analysis. It is worth to note that classical approach for the synthesis of 4H-pyrane is through Knoevenagel condensation of aldehyde with β-dicarbonyl compound and subsequent Michael addition with another β-dicarbonyl compound. Five-substituted-4H-pyrans are generally formed. But the synthesis of trisubstituted-4H-pyrans is somewhat limited [22].

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RESULTS AND DISCUSSION

Intrigued by this result, the reaction was carried out under various conditions, and the results are shown in Table **1**. Treatment of 3-butyn-2-one **1a** with 4-nitrobenzaldehyde **2a** in the presence of DMAP and 2,4-pentanedione for 12 h afforded **4a** in 84% yield (Table **1**, entry 1). Since 2,4-pentanedione was not involved in the product, the reaction was performed without it. However, a lower yield of the product (59%) was obtained in the absence of 2,4-pentanedione. Prolonged reaction time of 24 h gave 78% yield (Table **1**, entriy 3). These results imply 2,4-pentanedione mediated this hetero-cyclization reaction. When the temperature was lowered to 0 ˚C, the yield was decreased to 64% (Table **1**, entry 4). THF or toluene as a solvent was usable, and gave moderate yield. However, Et_2O and CH_3CN gave trace amount of the product. Other nitrogen Lewis bases were then examined in the reaction of 4-nitrobenzaldehyde with 3-butyn-2-one in the presence of 2,4-pentanedione. It was found that pyridine, DABCO and Et_3N are less efficient catalysts and gave the product **4a** in 62%, 65% and 49% yields, respectively. No reaction occurred when the reaction was catalyzed by DBU. Thus, the optimal reaction conditions were established for this reaction using 10 mol% DMAP and 50 mol% 2,4-pentanedione to perform the reaction in CH_2Cl_2 at room temperature for 12 h.

Under optimized reaction conditions, we next examined the reaction of other aromatic aldehydes with 3-butyn-2-one, and these results are summarized in Table **2**. It was found that the reactions of aromatic aldehydes with a strong electron-withdrawing group, such as NO_2 and CN groups, on the aromatic ring afforded the corresponding products in good yields. But the substituents of chloro-, bromo-, methyl-, methoxyl, and CF_3 groups at *para* position of their aromatic rings gave 1,3,5-triacetylbenzene along with trace amount of the desired products **4**. The product of 1,3,5-triacetylbenzene was formed through cyclotrimerization of 3-butyn-2-one mediated by DMAP and 2,4-pentanedione [23]. Unfortunately, these arylaldehydes afforded small amount of products **4** (<10%), when the reactions were carried out in

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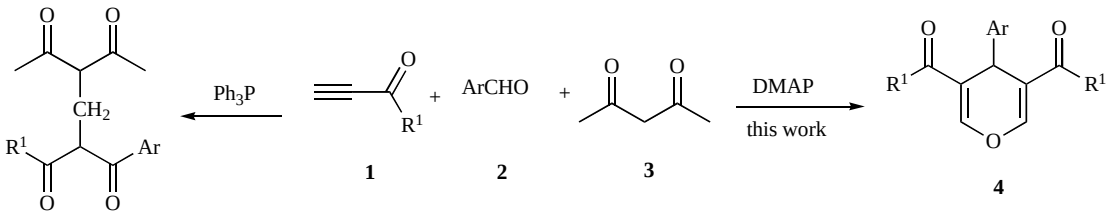
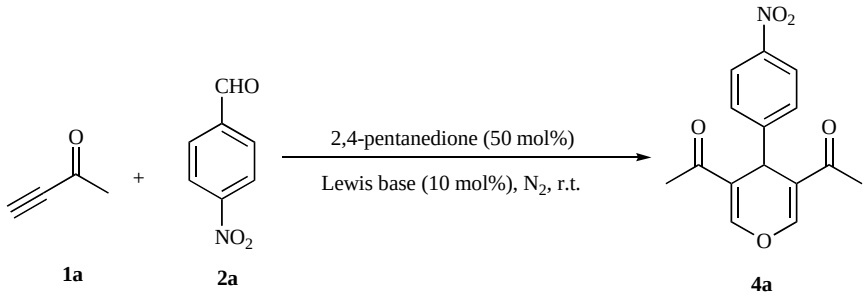


Scheme 1. Reactions of aldehydes with acetylenic ketones and 2,4-pentanedione catalyzed by Lewis bases.

Table 1. Reaction of 3-Butyn-2-one and 4-Nitrobenzaldehyde under Various Conditions[a]



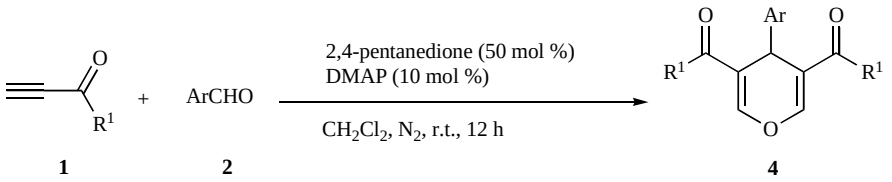
entry	Lewis base	Solvent	Time/h	Yield (%)[b]
1	DMAP	CH_2Cl_2	12	84
2	DMAP	CH_2Cl_2	12	59[c]
3	DMAP	CH_2Cl_2	24	78[c]
4	DMAP	CH_2Cl_2	24	64[d]
5	DMAP	THF	12	67
6	DMAP	toluene	12	53
7	DMAP	Et_2O	12	Trace
8	DMAP	CH_3CN	12	Trace
9	Pyridine	CH_2Cl_2	12	62
10	DABCO	CH_2Cl_2	12	65
11	Et_3N	CH_2Cl_2	12	49
12	DBU	CH_2Cl_2	12	NR[e]

[a]Unless otherwised specified, all of the reactions were carried out in the presence of 2,4-pentanedione (50 mol%) and Lewis base (10 mol%) based on acetylenic ketone.
[b]Yields after purification by silica gel column chromatography.
[c]Without 2,4-pentanedione.
[d]at 0 ˚C.
[e]NR = no reaction.

the absence of 2,4-pentanedione. These results demonstrate that, active arylaldehyde with NO_2 or CN group is of great importance for the formation of product **4**. It should be noted that 4-methyl-3-nitrobenzaldehyde gave the corresponding product **4e** in 8% yield under the typical conditions. The yield was increased to 46%, when the reaction was performed without 2,4-pentanedione. When 1-phenylprop-2-yn-1-one as an aromatic acetylenic ketone instead of 3-butyn-2-one was subjected to this reaction, the corresponding products **4f-i** were obtained in moderate yields along with the byproduct of 1,3,5-tribenzoylbenzene, which was formed through cyclotrimerization of 1-phenylprop-2-yn-1-one.

A tentative mechanism to account for this new cyclization is outlined in Scheme **2**. DMAP acts as a nucleophilic promoter to initiate the reaction and produce zwitterionic intermediate **5**. The intermediate **5** adds to aldehyde to form **6**, which generates **7** through an intramolecular conjugate addition of the oxygen anion to the β carbon of ketone. The intermediate **7** might be transformed into oxetene **8** by elimination of DMAP. The unstable oxetene **8** generates a polar intermediate **9** [24], followed by cycloaddition with a second acetylenic ketone to give the product **4** [25]. The 2,4-pentanedione might serve as Brønsted acid to activate the conjugate addition step for the formation of intermediate **6**. The mechanistic details of this reaction need further investigation.

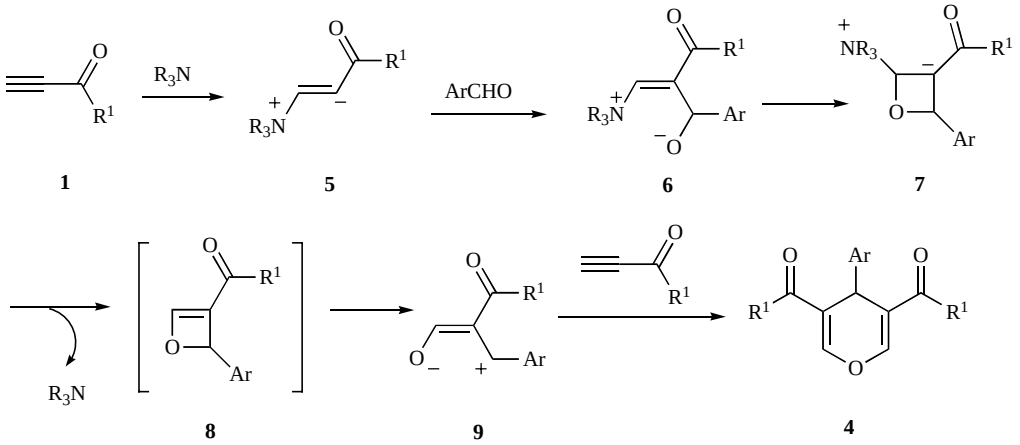
Table 2. Reactions of Aldehydes and Acetylenic Ketones



1 **2** **4**

Entry	R_1	Ar	Product	Yield (%)[a]
1	Me	4-$NO_2C_6H_4$	**4a**	84
2	Me	3-$NO_2C_6H_4$	**4b**	82
3	Me	2-$NO_2C_6H_4$	**4c**	80
4	Me	4-CNC_6H_4	**4d**	81
5	Me	3-NO_2-4-$CH_3C_6H_3$	**4e**	8 (46[b])
6	Ph	4-$NO_2C_6H_4$	**4f**	56
7	Ph	3-$NO_2C_6H_4$	**4g**	59
8	Ph	4-CNC_6H_4	**4h**	55
9	Ph	2-CNC_6H_4	**4i**	33

[a]Yields after purification by silica gel column chromatography.
[b]without 2,4-pentanedione.



1 **5** **6** **7** **8** **9** **4**

Scheme 2. Possible mechanism for the formation of 3,4,5-trisubstituted-4H-pyrans.

CONCLUSION

In summary, we have described a new cycloaddition of aryl aldehydes with acetylenic ketones mediated by 4-dimethylaminopyridine and 2,4-pentanedione. The reactions of 3-butyn-2-one with active aryl aldehydes containing NO_2 and CN groups on their aromatic rings gave 3,4,5-trisubstituted-4H-pyrans in good yields under mild conditions. 1-Phenylprop-2-yn-1-one as an aromatic acetylenic ketone afforded the desired products in moderate yields due to the competing cyclotrimerization reaction.

EXPERIMENTAL SECTION

General

All reactions were conducted under nitrogen atmosphere in oven-dried glassware with magnetic stirring. Chromatographic purification was performed on silica gel (100~200 mesh) and analytical thin layer chromatography (TLC) on silica gel 60-F_{254}, which was detected by fluorescence. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured with a Bruker AC 300 spectrometer using tetramethylsilane (TMS) as an internal standard. ^{1}H NMR data are reported as follows: δ, chemical shift; coupling constants (*J* are given in Hertz, Hz) and integration. High resolution mass spectra were obtained with a Micromass GCT-TOF mass spectrometer. IR spectra were recorded as thin films on a Perkin-Elmer FT210 spectrophotometer.

General Procedure for the Synthesis of 4H-Pyrans

To a solution of acetylenic ketone (0.3 mmol), 2,4-pentanedione (0.15 mmol) and aromatic aldehyde (0.3

mmol) in dry CH_2Cl_2 (2 mL) was added DMAP (0.03 mmol) at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (10:1 petroleum ether/EtOAc) to give the desired product.

3,5-diacetyl-4-(4-nitrophenyl)-4H-pyran (4a)

^{1}H-NMR: δ = 8.03 (d, J = 8.7 Hz, 2H), 7.58 (s, 2H), 7.42 (d, J = 8.7 Hz, 2H), 4.91 (s, 1H), 2.13 (s, 6H); ^{13}C-NMR: δ = 194.4, 150.8, 149.8, 146.9, 129.7, 123.6, 121.5, 33.8, 25.6; IR (neat; cm^{-1}): *v* 1693, 1597, 1519, 1346; HRMS (EI): calcd for $C_{15}H_{13}NO_5$ (M^+), 287.0794; found 287.0790.

3,5-diacetyl-4-(3-nitrophenyl)-4H-pyran (4b)

^{1}H-NMR: δ = 7.95-7.92 (m, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.60 (s, 2H), 7.37-7.31 (m, 1H), 4.92 (s, 1H), 2.14 (s, 6H); ^{13}C-NMR: δ = 194.4, 149.9, 148.6, 145.8, 135.9, 128.9, 123.0, 122.1, 121.5, 33.6, 25.6; IR (neat; cm^{-1}): *v* 1672, 1602, 1529. HRMS (EI): calcd for $C_{15}H_{13}NO_5$ (M^+), 287.0794; found 287.0795.

3,5-diacetyl-4-(2-nitrophenyl)-4H-pyran (4c)

^{1}H-NMR: δ = 7.75-7.53 (m, 1H), 7.72 (s, 2H), 7.53-7.38 (m, 1H), 7.30-7.20 (m, 2H), 5.67 (s, 1H), 2.19 (s, 6H); ^{13}C-NMR: δ = 195.0, 150.1, 149.8, 137.4, 132.6, 131.3, 127.8, 124.8, 121.1, 29.9, 25.9; IR (neat; cm^{-1}): *v* 1672, 1602, 1529. HRMS (EI): calcd for $C_{15}H_{13}NO_5$ (M^+), 287.0794; found 287.0791.

3,5-diacetyl-4-(4-cyanophenyl)-4H-pyran (4d)

^{1}H-NMR: δ = 8.04 (d, *J* = 8.7 Hz, 2H), 7.58 (s, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 4.92 (s, 1H), 2.13 (s, 6H); ^{13}C-NMR: δ = 194.4, 150.8, 149.8, 146.8, 129.7, 129.5, 123.6, 121.5, 33.8, 25.6; IR (neat; cm^{-1}): *v* 1656, 1600, 1515. HRMS (EI): calcd for $C_{16}H_{13}NO_3$ (M^+), 267.0895; found, 267.0898.

3,5-diacetyl-4-(4-methyl-3-nitrophenyl)-4H-pyran (4e)

^{1}H-NMR: δ = 7.77 (s, 1H), 7.65 (s, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 4.92 (s, 1H), 2.52 (s, 3H), 2.22 (s, 6H); ^{13}C-NMR: δ = 194.6, 149.8, 143.4, 134.3, 132.6, 124.3, 121.7, 33.2, 25.8, 20.3; IR (neat; cm^{-1}): *v* 1661, 1598, 1525. HRMS (ESI): calcd for $C_{16}H_{15}NO_5$ $(M+Na)^+$, 324.0842; found, 324.0837.

3,5-dibenzoyl-4-(4-nitrophenyl)-4H-pyran (4f)

^{1}H-NMR: δ = 8.17 (d, *J* = 8.7 Hz, 2H),7.66 (d, *J* = 8.7 Hz, 2H), 7.63-7.51 (m, 6H), 7.45-7.39 (m, 4H), 7.38 (s, 2H), 5.47 (s, 1H); ^{13}C-NMR: δ = 193.56, 151.4, 150.6, 147.0, 137.7, 132.4, 129.6, 128.79, 128.74, 123.9, 120.1, 35.5; IR (neat; cm^{-1}): *v* 1641, 1597, 1517, 1345. HRMS (EI): calcd for $C_{25}H_{17}NO_5$ (M^+), 411.1107; found, 411.1094.

3,5-dibenzoyl-4-(3-nitrophenyl)-4H-pyran (4g)

^{1}H-NMR: δ = 8.28 (s, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.57-7.48 (m, 6H), 7.57-7.42 (m, 5H), 7.39 (s, 2H), 5.48 (s, 1H); ^{13}C-NMR: δ =193.6, 151.5, 148.8, 145.6, 137.8, 135.8, 132.4, 129.4, 128.8, 128.7, 122.9, 122.3, 120.1, 35.2; IR (neat; cm^{-1}): *v* 1647, 1597, 1528. HRMS (EI): calcd for $C_{25}H_{17}NO_5$ (M^+), 411.1107; found, 411.1104.

3,5-dibenzoyl-4-(4-cyanophenyl)-4H-pyran (4h)

^{1}H-NMR: δ = 8.17 (d, *J* = 8.4 Hz, 2H),7.66 (d, *J* = 8.7 Hz, 2H), 7.56-7.51 (m, 6H), 7.45-7.39 (m, 4H), 7.38 (s, 2H), 5.47 (s, 1H); ^{13}C-NMR: δ = 193.5, 151.4, 150.6, 147.1, 137.8, 132.4, 129.6, 128.8, 128.7, 123.9, 120.2, 120.1, 35.5; IR (neat; cm^{-1}): *v* 1629, 1597, 1516; HRMS (EI): calcd for $C_{26}H_{17}NO_3$ (M^+), 391.1208; found, 391.1210.

3,5-dibenzoyl-4-(2-cyanophenyl)-4H-pyran (4i)

^{1}H-NMR: δ = 7.71 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 1H), 7.58-7.51 (m, 6H), 7.46-7.39 (m, 6H), 7.37 (s, 2H), 5.40 (s, 1H); ^{13}C-NMR: δ = 193.5, 151.4, 145.0, 137.8, 133.8, 132.4, 131.9, 130.9, 129.3, 128.8, 128.7, 120.3, 118.9, 112.86, 35.1; IR (neat; cm^{-1}): *v* 1648, 1597, 1522. HRMS (EI): calcd for $C_{26}H_{17}NO_3$(M^+), 391.1208; found, 391.1211.

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