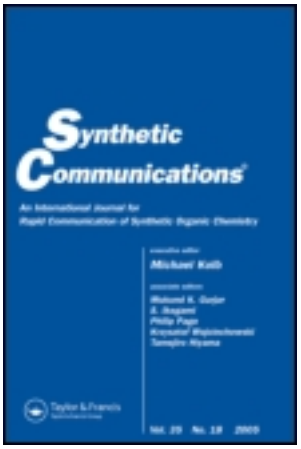

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Efficient One-Pot Synthesis of 4-Aroyl-2-pyrones: Nucleophilic Addition of Active Methylene Groups to 1,2-Diaroylacetylenes

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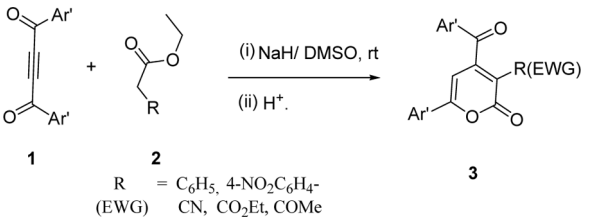
EFFICIENT ONE-POT SYNTHESIS OF 4-AROYL-2-PYRONES: NUCLEOPHILIC ADDITION OF ACTIVE METHYLENE GROUPS TO 1,2-DIAROYLACETYLENES

Ravi Shankar, Harsha Shukla, Uma Sharan Singh, Vinay Thakur, and K. Hajela

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow, India

GRAPHICAL ABSTRACT



Abstract *An efficient synthesis of 3,6-disubstituted-4-aroyl-2-pyrones in a single-step reaction through Michael addition of 1,2-diaroylacetylenes with active methylene compounds in the presence of NaH in dimethylsulfoxide at room temperature is reported. The structures have been confirmed by spectral data analyses.*

Keywords 4-Aroyl-2-pyrones; 1,2-diaroylacetylenes; Michael addition

INTRODUCTION

Synthetic compounds as well as simple and complex natural products[1] possessing a 2-pyrone moiety exhibit an incredibly diverse range of biological activities such as anticancer,[2] antimicrobial,[3] phytotoxic,[4] and COX-2 inhibitory activities.[5] In organic synthesis, 2-pyrones find application as dienes in Diels–Alder reactions[6] and as precursors to many carbocyclic and heterocyclic systems.[7] Very recently, 4-hydroxy-2-pyrones have been shown to be potent HIV-1 protease inhibitors,[8] and consequently, the syntheses of 2-pyrones with different substitution patterns presents an interesting challenge.

A number of methods for the introduction of substituents at different positions of the 2-pyrone ring have been reported. Most of these methods involve the

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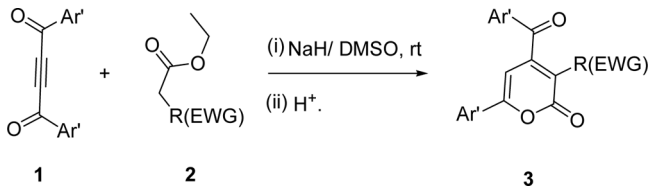
lactonization of 4-alkynoic acids promoted by palladium or by electrophilic reagents.[9] In many cases, these procedures lead to alkylidene butenolides instead of pyrones, and when carried out with nonsymmetric alkynes two 2-pyrone regioisomers may be obtained.[10] Recently, a potassium carbonate–catalyzed 1,4-addition of malonic esters to allenic ketones forming 2-pyrones has been reported.[11]

RESULTS AND DISCUSSION

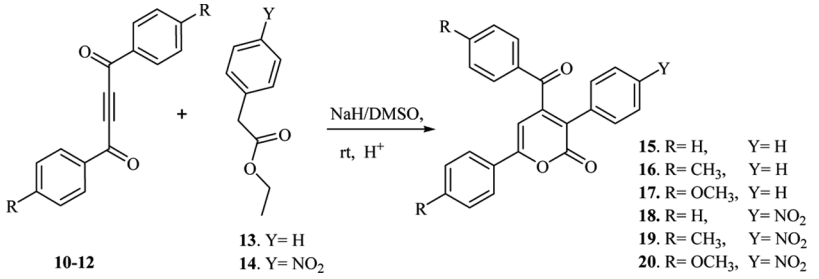
As part of our research on syntheses of new chemical leads with estrogen receptor modulating activities, we felt the need for a 4-aroyl-3,6-disubstituted 2-pyrone system as a suitable building block that could be modified with desirable substituents to target molecules. A survey of literature revealed only one reference reporting[12] Michael addition of mandelic acid enolate to *trans*-1,2-diaroylethenes and transformation of the resulting intermediate into 4-aroyl-2-pyrones.The process is tedious and required the formation of cumbersome intermediate 1,3-dioxolan-4-ones. It is reported in the literature that 3,4,6-triarylpyrone derivatives can be prepared by condensation of esters of phenyl acetic acid with 1,3-diaryl propyne-2-ones in the presence of a base in dimethylsulfoxide (DMSO) at room temperatute.[13] We envisaged that the same reaction conditions could be applied to condensing diaroylacetylene with an active methylene compound and found that the reaction between 1,4-diphenyl-but-2-yne-1,4-dione and diethylmalonate (1:1 equiv) using sodium hydride in dimethylformamide (DMF) at room temperature proceeded very smoothly, giving the desired 4-aroyl-2-pyrone in very good yield. In this communication, we describe this novel one-step reaction for the preparation of 4-aroyl-2-pyrones **3** by nucleophillic addition of 1,2-diaroylacetylenes **1** to active methylene groups **2** (Scheme 1).

The target molecules, 3,6-diaryl-4-aroyl-pyran-2-ones (**15–20**), were obtained in moderate to good yields (22–62%) by condensation of 1,2-diaroylacetylenes (**10–12**) with 4-substituted-phenylacetic acid esters (**13, 14**) in the presence of a base such as sodium hydride at 25 °C. All the reactions were complete in 1 h. Quenching of the reaction mixture with 20% aqueous HCl mostly precipitated solids (in some cases, dark-colored viscous liquids were obtained), which were suitably crystallized or purified by silica gel or basic alumina column chromatography to give the desired pure compounds in good yields (Scheme 2).

To explore the scope of this cyclization strategy, 1,2-diaroylacetylenes (**10**–**12**) were reacted with different active methylene groups such as diethylmalonate, ethylcyanoacetate, and ethylacetoacetate (**21–23**) under the same reaction conditions as described previously. The desired 4-aroyl-2-pyranones (**24–32**) were obtained in yields of 80–90% in all cases (Scheme 3).



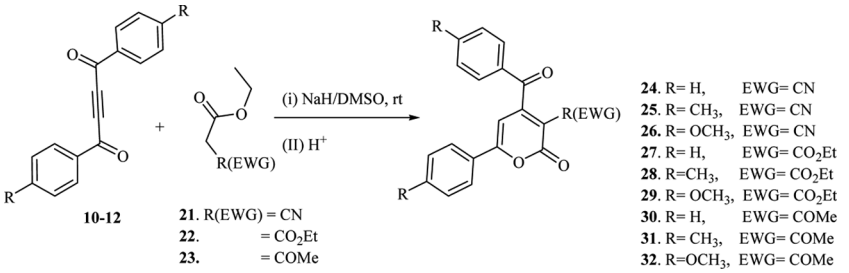
Scheme 1. Synthesis of 3,6-disubstituted-4-aroyl-2-pyrones.



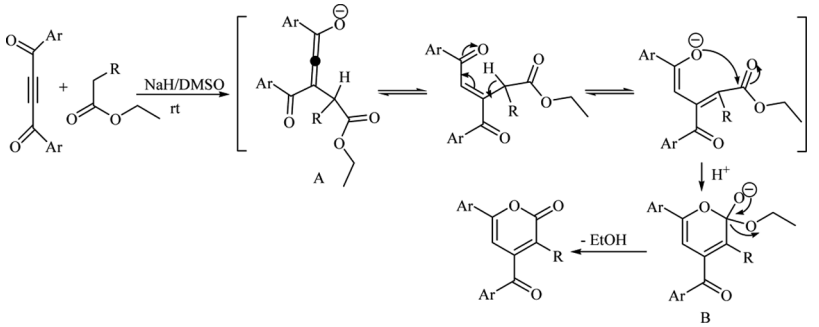
Scheme 2. Synthesis of 3,6-diaryl-4-aroyl-2-pyrones.

Among the bases tested, sodium hydride was found to be the most effective. Other bases such as potassium carbonate, sodium ethoxide, or potassium *t*-butoxide yielded inseparable reaction mixtures from which the desired compounds could be isolated in very poor yields. Changing the solvent to DMF or 1,4-dioxane prolonged the reaction times several fold.

A plausible reaction mechanism is shown in Scheme 4. The first step in the reaction cascade involves the attack of carbanion of the active methylene compound of 1,2-diaroylacetylene, forming the allene adduct (**A**), which undergoes intramolecular cyclization, forming **B**. Facile elimination of EtOH under acidic conditions gave

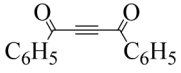
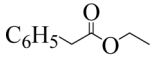
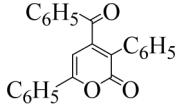
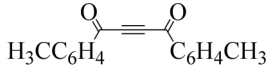
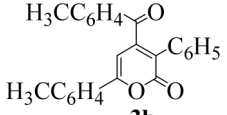
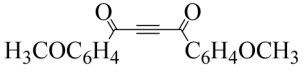
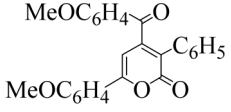
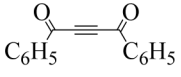
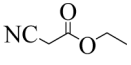
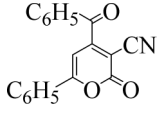
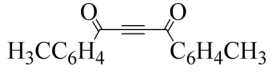
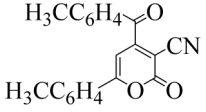


Scheme 3. Synthesis of 3-substituted-6-aryl-4-aroyl-2-pyrones.



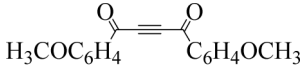
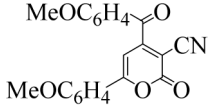
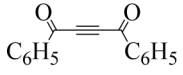
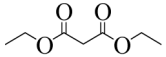
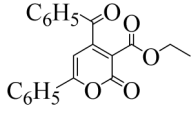
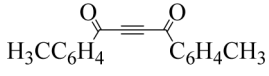
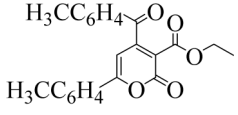
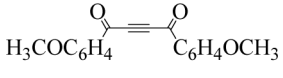
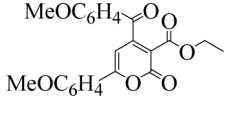
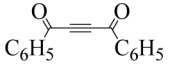
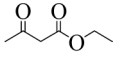
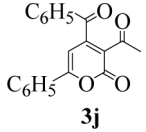
Scheme 4. A plausible mechanism for the synthesis of 3,6-disubstituted-4-aroyl-2-pyrones.

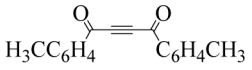
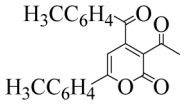
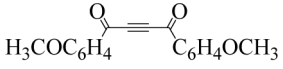
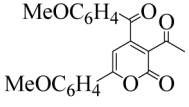
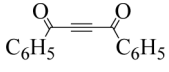
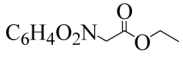
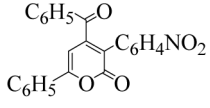
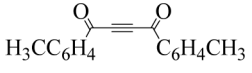
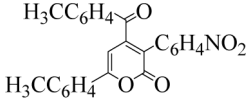
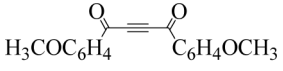
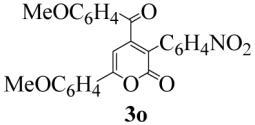
Table 1. Synthesis of substituted 4-aroyl-pyran-2-ones

Entry	Diaroylacetylenes	Nucleophile	Product	Time (min)	Mp (°C)	Yield (%)
1	 **1a**	 **2a**	 **3a**	45	178–179	60
2	 **1b**		 **3b**	45	200–202	50
3	 **1c**		 **3c**	40	190–192	50
4	 **1a**	 **2b**	 **3d**	45	115–116	72
5	 **1b**		 **3e**	40	145–148	75

(*Continued*)

Table 1. Continued

Entry	Diaroylacetylenes	Nucleophile	Product	Time (min)	Mp (°C)	Yield (%)
6	 **1c**		 **3f**	40	112–114	77
7	 **1a**	 **2c**	 **3g**	50	150–152	82
8	 **1b**		 **3h**	55	138–140	84
9	 **1c**		 **3i**	50	125–126	88
10	 **1a**	 **2d**	 **3j**	20	135–137	73

11	 **1b**		 **3k**	20	127–130	70
12	 **1c**		 **3l**	20	117–119	75
13	 **1a**	 **2c**	 **3m**	30	130–132	63
14	 **1b**		 **3n**	30	120–121	60
15	 **1c**		 **3o**	30	115–116	75

the desired 4-aroyl-2-pyrones. The yield of pyrones was excellent when electron-withdrawing groups were present in the nucleophiles.

The order of reactivity was found to be diethylmalonate > ethylcyanoacetate > ethylacetoacetate > ethyl 4-nitrophenylacetate > ethylphenylacetate. The reaction was not successful with either diethyl succinate or ethyl-4-methoxyphenylacetate bearing electron-donating groups. Under the optimized conditions, a number of compounds with active methylene groups (**2a–e**) reacted with simple and substituted 1,2-diaroylacetylenes (**1a–c**) forming 3,6-disubstituted-4-aroyl-2-pyrones (**3a–o**) in excellent yields (Table 1).

CONCLUSIONS

We report for the first time a facile, one-step synthesis of 3,6-disubstituted-4-aroyl-2-pyrones. The reaction is simple, fast, and convenient. Excellent yields of the products make it attractive for large-scale synthesis of this potentially biologically active class of molecules.

EXPERIMENTAL

General melting points are uncorrected and were determined in capillary tubes on a hot-stage apparatus containing silicon oil. Infrared (IR) spectra were recorded using a Perkin-Elmer RX I Fourier transform (FT)–IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a 300- or 200-MHz FT spectrometer, using tetramethylsilane (TMS) as an internal standard (chemical shifts in δ values, J in Hz). The electrospray ionization–mass spectra were recorded through direct flow injections in a Merck M-8000 liquid chromatography–mass spectroscopy (LCMS) system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer.

Representative Procedure

A solution of the ethyl phenyl acetate (**2a**, 164 mg, 1 mmol) was added to a suspension of NaH (60% oil dispersion, 32.8 mg, 1.2 mmol) in dry DMSO (15 ml), and the reaction mixture was allowed to stir for 30 min. A solution of 1,2-diaroylacetylene (**1c**, 294 mg, 1 mmol) in DMSO was added dropwise, and the mixture was stirred at room temperature for another 45 min. Within this period, the reaction was found to be complete as checked by thin-layer chromatography (TLC). It was quenched with 20% aqueous HCl, and the precipitated solid was filtered, washed with water, and purified by column chromatography. Finally, crystallization from ethanol gave **3c** as a white crystalline solid.

Spectral Data for Selected Compounds

Compound 3c. Mp 190–192 °C; ^{1}HNMR (300 MHz, $CDCl_3$): **δ** 3.85 (s, 3H), 3.90 (s, 3H), 6.65 (s, 1H), 6.83 (d, 2H, $J = 8.9$ Hz), 6.99 (d, 2H, $J = 8.9$ Hz), 7.23 (m, 3H), 7.37 (m, 2H), 7.76 (d, 2H, $J = 8.9$ Hz),7.87 (d, 2H, $J = 8.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.45, 99.63, 114.10, 114.45, 127.44, 128.14, 128.60, 129.21,

129.88, 132.08, 133.61, 134.90, 135.88, 136.84, 139.25, 141.87, 160.06, 164.34, 196.67. ESI: 413 ($M^+ + 1$). HRMS calculated for $C_{26}H_{20}O_5$: 412.1311; measured: 412.1302.

Compound 3d. Mp 172–175 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1H), 7.54 (m, 5H), 7.57 (m, 1H), 7.92 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.63, 125.23, 127.80, 127.93, 127.96, 131.27, 133.21, 157.16, 163.28, 191.37. ESI: 302($M^+ + 1$). HRMS calcd. for $C_{19}H_{11}NO_3$: 303.0895; measured: 303.0903.

Compound 3h. Mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, 3H), 2.45 (s,6H), 4.10 (q, 2H), 6.61 (s, 1H), 7.31 (d, 2H, $J = 8.9$ Hz), 7.33 (d, 2H, $J = 8.9$ Hz), 7.79 (d, 2H, $J = 8.9$ Hz), 7.81 (d, 2H, $J = 8.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.27, 20.15, 20.58, 60.65, 98.13, 125.22, 126.06, 128.08, 128.48, 130.59, 142.24, 144.44, 157.56, 191.15. ESI: 377 ($M^+ + 1$), 331(M^+-C_2H_5OH). HRMS calculated for $C_{23}H_{20}O_5$: 376.1311; measured: 376.1289.

Compound 3j. Mp 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 6.76 (s, 1H), 6.82 (d, 2H, $J = 6.7$ Hz), 7.05 (d, 2H, $J = 6.7$ Hz), 7.24 (d, 2H, $J = 6.7$ Hz), 7.64 (d, 2H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.12, 105.36, 120.86, 123.70, 127.00, 127.52, 127.76, 128.06, 129.14, 132.32, 135.96, 137.46, 149.46, 158.09, 188.55. ESI: 318 ($M^+ + 1$). HRMS calculated for $C_{20}H_{15}O_4$: 319.09703 ($M^+ + 1$); measured: 319.09872.

Compound 3n. ^{1}H NMR (300 MHz, $CDCl_3$): 2.36 (s, 3H), 2.43 (s, 3H), 7.04 (s, 1H), 7.15 (d, 2H, $J = 8.04$), 7.57 (d, 2H, $J = 8.58$), 7.66 (d, 2H, $J = 8.0$ Hz), 7.92 (m, 2H), 8.06 (d, 2H, $J = 8.07$ Hz), 8.21 (d, 2H, $J = 8.58$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 21.62, 21.75, 96.16, 122.85, 123.72, 128.99, 129.22, 129.44, 129.99, 130.96, 133.74, 141.58, 143.91, 144.62, 145.00, 147.90, 165.75, 194.88. ESI: 426 ($M^+ + 1$).

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