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An efficient and improved synthesis of 1,5-diketones: versatile conjugate addition of nucleophiles to α,β-unsaturated enones and alkynones ☆

Ravi Shankar, Ashok K. Jha, Uma Sharan Singh and K. Hajela*

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, UP, India

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Abstract—Several 1,5-diketones have been prepared in good to excellent yields by versatile conjugate addition of nucleophiles such as cyclic or acyclic ketones, amines and thiols to α,β-unsaturated enones and alkynones, in the presence of catalytic amounts of 10% aq NaOH, TBAI and DMSO at ambient temperature. The choice of solvent and phase-transfer catalyst played a critical role in improving the reaction rate and yields of the products.

In the manufacture of pharmaceutical targets, increasing attention is now being paid to simplification and improvement of the existing methods. The conjugate addition of active enolates and other nucleophiles to α,β-unsaturated enones is an efficient method of C–C bond formation and has wide application in organic synthesis.[1] The reaction has been widely explored using a variety of expensive catalysts, both acidic and basic, such as $TiCl_4$,[2] $InCl_3$,[3] $FeCl_3{\cdot}H_2O$,[4] lanthanides,[5] $Bi(NO_3)_3$,[6] $Bi(OTf)_3$,[7] $Cu(BF_4)_2$,[8] iodine[9] and others.[10] However, the use of toxic and expensive metal catalysts is not economically viable and limits their use in large scale production and also conflicts with aspects of 'green chemistry'.

In our endeavours towards the synthesis of some novel tetracyclic compounds as selective estrogen receptor agonists and antagonists, we required several 1,5-diketones which formed essential intermediates to be elaborated to the desired target molecules. This led us to explore the use of aqueous sodium hydroxide to catalyze addition to α,β-unsaturated enones (1,3-diaryl alkenones) of cyclic or acyclic ketones. Typically, the reaction is reported to occur in the presence of alkali metal alkoxides as catalysts, using hydrophilic solvents and long reaction times sometimes extending into days. Since the reaction is reversible, long reaction times can seriously affect the yield.

In this letter, we report conjugate additions to 1,3-diaryl alkenones of both cyclic and acyclic ketones and of various other nucleophiles using a catalytic amount of 10% aq sodium hydroxide, tetra-*n*-butylammonium iodide in dimethyl sulfoxide (DMSO) as solvent. Although DMSO has been little exploited in such additions, it is reported to have a profound rate accelerating effect in other situations.[11,12]

The reactions were completed within 15–30 min as monitored by TLC and the products isolated either through precipitation by quenching with water or extraction with ethyl acetate. The yields of the products were between 70% and 85%. The reaction was initially performed by dissolving and stirring the reactants in ethanol using 50% aq sodium hydroxide without any catalyst at room temp. But, even after stirring for 48 h, the reaction was incomplete and only poor yields of 1,5-diketones were obtained. Changing the solvent to dioxane, DMF or THF caused no improvement in the yields. Addition of the phase-transfer catalyst tetra-*n*-butylammonium bromide improved the yields moderately. However, when the reaction was carried out in DMSO as solvent, the reaction proceeded very smoothly and was completed in 15–30 min depending on the reactants. TLC

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* Corresponding author. Tel.: +91 522 2612411/18 (PABX) Extn: 4463; fax: +91 522 2623405; e-mail: hajelak@yahoo.com

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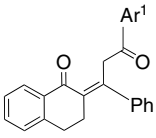
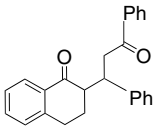
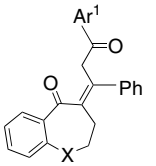
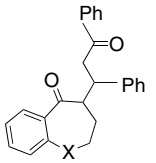
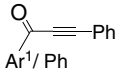
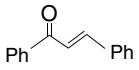
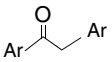
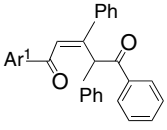
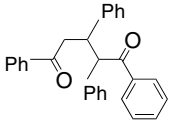
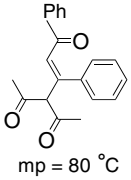
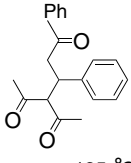
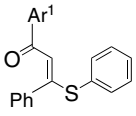
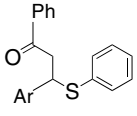
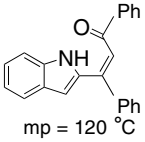
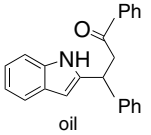
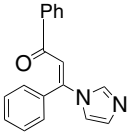
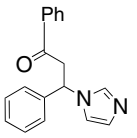
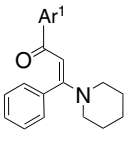
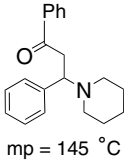
of the reaction mixtures showed one major single spot and the products were isolated in pure form through column chromatography. The diketones of examples 1–3 (Table 1) were obtained as diastereomeric mixtures and showed overlapping spots on TLC when viewed under UV irradiation. ^{1}H NMR spectroscopy of the diastereoisomers showed a trans:cis ratio of 60:40. The reaction worked well both with cyclic and acyclic

Table 1.

	Michael acceptor	Michael donor	Product		Time (min)		Yield (%)	
			A	B	A	B	A	B
1			 mp =115 °C	 oil	30	25	52	78
2		 X= CH_2, S , O	 oil, X= CH_2, S, O	 oil, X= CH_2, S, O	45	25	30–42	68–70
3	 **Alkynone** or  **Enone**		 mp =132 °C	 mp =105 °C	30	30	72	73
4			 mp = 80 °C	 mp = 125 °C	45	15	56	85
5			 mp =108 °C	 mp = 120 °C	25	5	68	70
6			 mp = 120 °C	 oil	45	25	55	75
7			 oil	 oil	45	25	66	70
8			 oil	 mp = 145 °C	30	15	70	75

A = product with alkynone.
B = product with alkenone.
Ar^1 = 4-$MeOC_6H_4$.

ketones including tetralone, benzosuberone, benzoin and acetylacetone. The mildness of the reaction conditions prompted us to explore different nucleophiles like indole, imidazole, benzenethiol and piperidine (Table 1) and found the reaction to be equally efficient. Among different phase-transfer catalysts such as TBAF, TBAC, TBAB, TBAI and benzyltrimethylammoniun hydroxide solution (Triton B, 40% in water) that were used, tetra-*n*-butylammonium iodide was found to give the best results.

The success with 1,3 diaryl alkenones prompted us to explore conjugate addition to alkynones. The reaction was carried out with 1,3-diaryl propynones under similar reaction conditions. However, with alkynones the reaction times were longer and the yields of diketones were also moderate ranging between 42% and 52% for the cyclic ketones, but with acyclic ketones, thiols and amines the yields were higher and ranged between 55% and 72%. Further, recovery of phenylacetylene and benzoic acid from column chromatography indicated decomposition of alkynones under prolonged basic conditions.

General experimental procedure: To a solution of benzenethiol (110 mg, 1 mmol) dissolved in dimethyl sulfoxide (5 ml) were added tetra-*n*-butylammonium iodide (10 mg) and 10% aq NaOH solution (0.5 ml). The mixture was stirred at rt for 30 min. Thereafter, 1-(4-methoxyphenyl)-3-phenyl-propynone (1 mmol, 236 mg) was added and the solution stirred for another 15 min. On completion of the reaction (TLC), the mixture was quenched with water (5 ml) resulting in precipitation of the product. Filtration, washing with water and recrystallization from benzene–hexane gave pure adduct **5A** (202 mg), yield; 68%, mp 108 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03, (d, $J = 9$ Hz, 2H), 7.25–7.03 (m, 11H), 6.92, (d, $J = 9$ Hz, 2H) and 3.88 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 187.8, 163.5, 161.1, 139.3, 134.6, 133.3, 131.8, 130.8, 129.3, 128.7, 120.5, 114.2, 110.0, 55.8. IR (KBr) cm^{-1} 1632, 1594, 1536, 1507–1440, 2843. HRMS: Calcd for $C_{22}H_{18}O_2S$: 346.1028, measured mass 346.1018. Reaction with 1,3-diphenyl propenone and benzenethiol gave adduct **5B** (220 mg), yield; 70%, mp 120 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (d, $J = 8.6$ Hz, 2H), 7.45–7.13 (m, 13H), 4.96 (t, $J = 14.2$ Hz, 1H), 3.65 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 187.8, 163.5, 161.1, 139.3, 134.6, 133.3, 131.8, 130.8, 129.4, 128.7, 127.9, 127.5, 120.5, 114.2, 55.8, 31.3. IR (KBr) cm^{-1} 1677, 1592, 1480–1450, 2903. HRMS: Calcd for $C_{21}H_{18}OS$: 318.1078, measured mass 318.1069.

In conclusion, we have successfully demonstrated a very efficient and mild conjugate addition of various nucleophiles to 1,3-diphenyl propenones or propynones by the use of only catalytic amounts of 10% aqueous sodium hydroxide in combination with TBAI in dimethyl sulfoxide. The ease of workup and good yields of diketone products are significant improvements over existing methods that chiefly employ expensive metal catalysts. Transformation of diketones into a new class of biological active compounds is in progress and will be published soon.

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