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Efficient synthesis of novel fluorinated bisarylmethylidenes of pyran-4-one and piperidin-4-one systems via aldol condensation reaction

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Abstract: A facile one-pot condensation of various fluorinated aldehydes with two heterocyclic ketones is developed by using catalytic quantities of $ZrOCl_2.8H_2O$ and sodium dodecyl sulfate under organocatalyzed aqueous conditions at ambient temperature. Consequently, efficient synthesis of several bisarylmethylidenes of two heterocyclic ketones is observed within relatively short time periods. Products precipitate in high yields in the reaction mixtures and are isolated by simple filtration.

Keywords: Aldol condensation, Organocatalysis, Aqueous medium, Heterocycles, Lewis acid catalysis.

Introduction

Aldol condensation reaction is arguably the most versatile pathway to access α,β-unsaturated carbonyl systems [1]. This reaction usually involves nucleophilic addition of an enolate to an aldehyde followed by removal of water from the intermediate β-hydroxy carbonyl to form a C=C bond conjugated with a C=O moiety [2], a structural fragment which presents in many synthetically and naturally occurring biologically important compounds [3-5]. An interesting group of these compounds are bisarylmethylidenes of cyclic ketones which are often synthesized via aldol condensation [6] and have various industrial and pharmaceutical applications [7-9]. These compounds can also be employed as appropriate precursors for other synthetic reactions [10]. Among various recent methods reported for the synthesis of bisarylmethylidene derivatives, we can highlight those which involve the use of heterogeneous conditions [11], Lewis acid catalysts [12], solvent-free conditions [13], and aqueous media [14].

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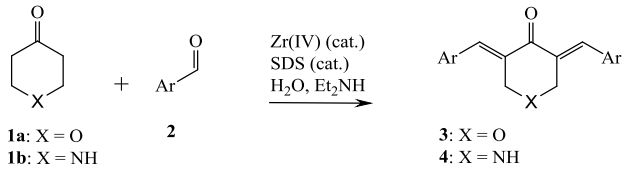
Zirconium based catalysts have been employed recently to facilitate various synthetic organic transformations [15]. In particular, Rawal *et al*. used sulfated zirconia for the synthesis of bisarylmethylidenes of cyclopentanone and cyclohexanone via cross aldol condensation reactions [16]. They prepared the catalyst under very high temperature conditions using a known procedure [17] and the condensation reaction itself required microwave irradiation. In connection with our ongoing program to develop the chemistry of heterocyclic compounds [18-19] and in the framework of our investigations on aldol condensation reactions [20-21], we were persuaded to study the possibility of synthesizing bisarylmethylidene derivatives of pyran-4-one and piperidin-4-one systems by zirconium based catalysts under relatively milder conditions. It is noteworthy to mention that the fluorinated organic structures are very important compounds in biological studies [22]. In particular, several heterocycles which contain fluorine atom are known for their unique medicinal and agricultural applications [23]. Thus, we would like herein to introduce a facile procedure for

the synthesis of various fluorinated derivatives of bisarylmethylidenes of two heterocyclic ketones **1a-b** (Scheme **1**). The method uses very mild aqueous conditions in the presence of catalytic amounts of $ZrOCl_2.8H_2O$ and sodium dodecyl sulfate (SDS) causing high yield conversion of the reactants to their respective products.



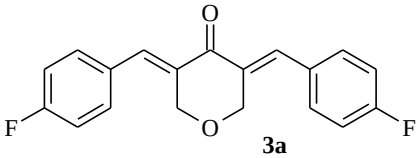
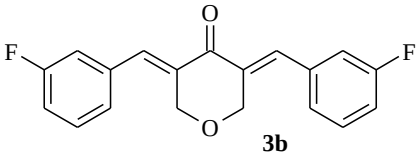
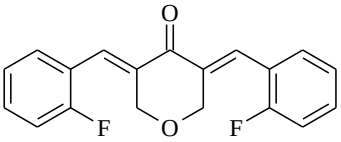
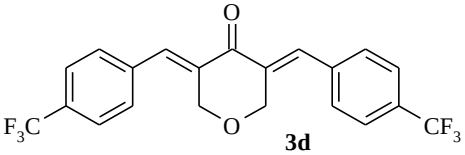
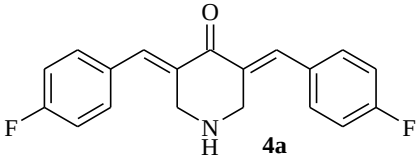
Scheme 1: Aqueous mediated synthesis of derivatives of **3-4**.

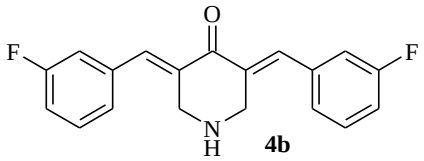
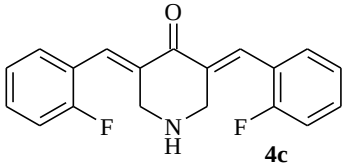
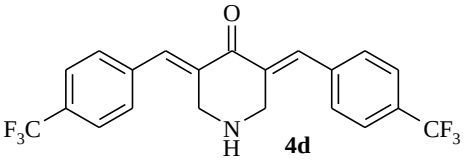
Results and discussion

Table **1** summarizes the results for the reactions of the two heterocyclic ketones **1a** and **1b** with four fluorinated aromatic aldehydes. We first optimized the conditions for the reaction of pyran-4-one **1a** with 4-fluorobenzaldehyde. Under the optimized conditions (Et_2NH, SDS, H_2O, $ZrOCl_2.8H_2O$), product **3a** was formed within 2 hours in 89% yield (entry 1). Use of other amines also caused formation of product **3a** but in lower yields. In the absence of an amine, the surfactant, or water, the reaction either halted completely or gave lower yields of the product in longer time periods. Alternatively, use of $ZrOCl_2.8H_2O$ led to faster progress of the reaction and spontaneous precipitation of the products. Use of other aromatic aldehydes bearing fluorine atom also led to comparable results (entries 2-4).

The procedure was further explored by applying the conditions to the reactions of piperidin-4-one **1b**. Condensation of the same fluorinated aldehydes with ketone **1b** led to high yield formation of products **4a-d** (entries 5-8), but in relatively longer time periods (6-8 hours). Again, due to the presence of the Lewis acid, products precipitated spontaneously in the reaction mixtures facilitating their separation and avoiding labor consuming and costly chromatographic purifications.

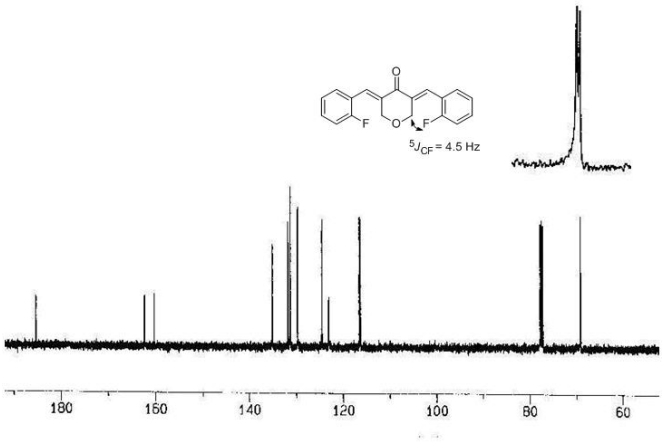
Table 1: One-pot synthesis of products **3-4**.

Entry	Reactants	Product	Yield (%)[a]
1	**1a** + 4-FC_6H_4CHO	 **3a**	89
2	**1a** + 3-FC_6H_4CHO	 **3b**	85
3	**1a** + 2-FC_6H_4CHO	 **3c**	88
4	**1a** + 4-$CF_3C_6H_4CHO$	 **3d**	90
5	**1b** + 4-FC_6H_4CHO	 **4a**	82

6	**1b** + 3-FC_6H_4CHO	 **4b**	85
7	**1b** + 2-FC_6H_4CHO	 **4c**	80
8	**1b** + 4-$CF_3C_6H_4CHO$	 **4d**	88

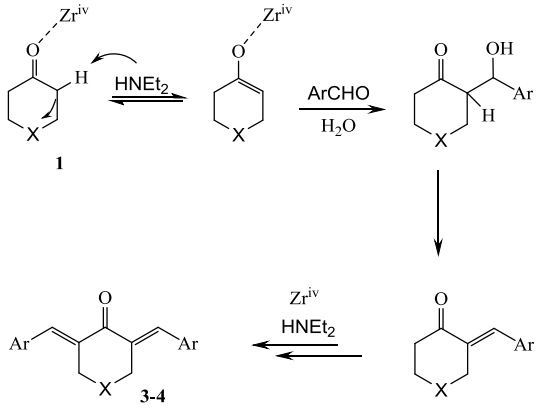
a) Isolated yield.

Structure of the products was elucidated based on their NMR spectra. In the case of products **3c** and **4c**, the ^{13}C NMR spectra were particularly helpful and provided a robust evidence for absolute stereochemistry of the exocyclic double bonds by showing a $^5J_{CF}$ of about 4 Hz for the endocyclic methylene carbons due to a through-space coupling with the *ortho* fluorine of the aldehyde residue (Scheme **2**). Although there are several reports on crystallographic structural determination of the related products [24-28], this observation provides a solid noncrystallographic documentation for assigning the geometry of the C═C bond in bisarylmethylidene products.



Scheme 2: An elucidative "through-space" carbon-fluorine coupling for **3c**.

Based on these results, a mechanistic pathway is proposed, as depicted in Scheme **3**. Initially, coordination of the C═O group to the Lewis acid facilitates deprotonation of the α hydrogen by the amine. The resulting enolate can then attack the starting aldehyde to obtain the aldol product. Further repeat of the process lead to formation of the final product. High solubility of the Lewis acid in water forces products to precipitate in the reaction mixtures.



Scheme 3: A plausible mechanism.

Conclusion

In summary, we have presented a general procedure merely devoted to the synthesis of fluorinated derivatives of bisarylmethylidenes of heterocyclic ketones. Reactions take place under organocatalyzed aqueous conditions using catalytic quantities of a surfactant and a Lewis acid. Under the conditions, products precipitate spontaneously. This allows easy separation of the products and avoids cumbersome and expensive purifications which are usually necessary in many other related procedures. We are currently applying the results to other synthetic transformations.

Experimental

Melting points are uncorrected. IR spectra are recorded using KBr disks on a Bruker Vector-22 infrared spectrometer. NMR spectra are obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz) as $CDCl_3$ solutions using TMS as internal standard reference. Elemental analyses are performed using a Thermo Finnigan Flash EA 1112 instrument. MS spectra are obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. TLC experiments are carried out on pre-coated silica gel plates using petroleum ether/EtOAc (5:1) as the eluent. All other chemicals are commercially available. Aldehydes are redistilled or recrystallized prior to being used.

General procedure:

A mixture of $ZrOCl_2.8H_2O$ (10 mol%) and SDS (25 mol%) in water (2.0 mL) is stirred at room temperature for 10 minutes. To this mixture is added an aldehyde (2.0 mmol), a ketone (**1a** or **1b**, 1.0 mmol), and Et_2NH (1.0 mmol) and the stirring is continued until TLC showed complete disappearance of the reactants. Products which precipitate spontaneously in the mixture are filtered and washed with brine (2 × 10 mL). The solid products were dried and then recrystallized from EtOAc and petroleum ether. Known products (**3c**, **4a**,**c**,**d**) are characterized based on the comparison of their physical and spectroscopic data with those reported in the literature [29-31]. New products are fully characterized by obtaining their ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, and mass spectra and their purity is confirmed by elemental analysis.

Spectral Data of New Products:

*(3E,5E)-3,5-Bis(4-fluorobenzylidene)dihydro-2H-pyran-4(3H)-one (**3a**):*

(278 mg, 89%), mp 186-188 °C (EtOAc). IR spectrum (KBr), ν, cm^{-1}: 1670 (C═O), 1602 (C═C), 1278 (Ar–F); ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm (*J*, Hz): 4.94 (4H, d, *J* = 1.0, OCH_2), 7.16 (4H, dd, *J* = 8.5, 8.5, H Ar), 7.34 (4H, dd, *J* = 5.5, 8.5, H Ar), 7.82 (2H, ap. s, ═CH); ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm (*J*, Hz): 68.9 (OCH_2), 116.3 (d, *J* = 21.5 Hz), 131.3 (d, *J* = 3.5 Hz), 132.8 (d, *J* = 8.5 Hz), 133.1 (d, *J* = 1.5 Hz), 135.8, 163.0 (d, *J* = 250.0, C–F), 185.6 (C═O); ^{19}F NMR spectrum ($CDCl_3$, 470 MHz) δ, ppm: -110.5; Mass spectrum (Ei, 70 eV), *m/z* (I_{rel}, %): 312 $[M]^+$ (3), 149 (7), 133 (100), 120 (25); Found, %: C 73.23; H 4.49. $C_{19}H_{14}F_2O_2$. Calculated, %: C 73.07; H 4.52.

*(3E,5E)-3,5-Bis(3-fluorobenzylidene)dihydro-2H-pyran-4(3H)-one (**3b**):*

(265 mg, 85%), mp 180-182 °C (EtOAc). IR spectrum (KBr), ν, cm^{-1}: 1676 (C═O), 1614 (C═C), 1210 (Ar–F); ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm (*J*, Hz): 4.94 (4H, s, OCH_2), 7.03 (2H, d, *J* = 9.5 Hz, H Ar), 7.11-7.14 (4H, m, H Ar), 7.43 (2H, dd, *J* = 9.0, 12.5 Hz, H Ar), 7.81 (2H, s, ═CH); ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm (*J*, Hz): 68.9 (OCH_2), 116.8 (d, *J* = 21.0 Hz), 117.3 (d, *J* = 21.5 Hz), 126.6 (d, *J* = 3.0 Hz), 130.7 (d, *J* = 8.0 Hz), 134.3, 135.6 (d, *J* = 2.5 Hz), 137.1 (d, *J* = 7.5 Hz), 163.0 (d, *J* = 246.0 Hz, C–F), 185.5 (C═O); ^{19}F NMR spectrum ($CDCl_3$, 470 MHz) δ, ppm: -112.5; Mass spectrum (Ei, 70 eV), *m/z* (I_{rel}, %): 312 $[M]^+$ (7), 162 (10), 133 (100), 120 (15); Found, %: C 73.33; H 4.57. $C_{19}H_{14}F_2O_2$. Calculated, %: C 73.07; H 4.52.

*(3E,5E)-3,5-Bis(4-(trifluoromethyl) benzylidene) dihydro-2H-pyran-4(3H)-one (**3d**):*

(371 mg, 90%), mp 204-206 °C (EtOAc). IR spectrum (KBr), ν, cm^{-1}: 1678 (C═O), 1614 (C═C), 1253 (CF_3); ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm (*J*, Hz): 4.96 (4H, d, *J* = 2.0 Hz, OCH_2), 7.45 (4H, d, *J* = 8.0 Hz, H Ar), 7.72 (4H, d, *J* = 8.0 Hz, H Ar), 7.88 (2H, ap. s, ═CH); ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm (*J*, Hz): 68.8 (OCH_2), 124.3 (q, *J* = 270.0 Hz, CF_3), 126.1 (q, *J* = 3.5 Hz), 130.9, 131.4 (q, *J* = 32.5 Hz, C–CF_3), 135.1, 135.5, 138.4, 185.4 (C═O); Mass spectrum (Ei, 70 eV), *m/z* (I_{rel}, %): 412 $[M]^+$ (12), 242 (25), 184 (100), 118 (85); Found, %: C 60.98; H 3.49. $C_{21}H_{14}F_6O_2$. Calculated, %: C 61.17; H 3.42.

*(3E,5E)-3,5-Bis(3-fluorobenzylidene)piperidin-4-one (**4b**):*

(265 mg, 85%), mp 159-161 °C (EtOAc). IR spectrum (KBr), ν, cm^{-1}: 1660 (C═O), 1607 (C═C), 1219 (Ar–F); ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm (*J*, Hz): 1.72 (1H, s, NH), 4.16 (4H, d, *J* = 2.0 Hz, NCH_2), 7.09-7.11 (4H, m), 7.19 (2H, d, *J* = 8.0 Hz), 7.39-7.44 (2H, m), 7.76 (2H, ap. S, ═CH); ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm (*J*, Hz): 48.4 (NCH_2), 116.4 (d, *J* = 21.0 Hz), 117.3 (d, *J* = 22.0 Hz), 126.7 (d, *J* = 2.5 Hz), 130.5 (d, *J* = 8.5 Hz), 135.1 (d, *J* = 2.0 Hz), 136.2, 137.6 (d, *J* = 7.5 Hz), 163.1 (d, *J* = 245.0 Hz, C–F), 188.0 (C═O); ^{19}F NMR spectrum ($CDCl_3$, 470 MHz) δ, ppm: -112.5; Mass spectrum (Ei, 70 eV), *m/z* (I_{rel}, %): 311 $[M]^+$ (12), 282 (42), 188 (18), 148 (49), 133 (100); Found, %: C 73.12; H 4.62. $C_{19}H_{15}F_2NO$. Calculated, %: C 73.30; H 4.86.

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