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Research Note

An efficient synthesis of monoarylidene derivatives of pyran-4-one and piperidin-4-one

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α,β-unsaturated ketones;
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Abstract. A room-temperature procedure is developed for the direct synthesis of monoarylidene derivatives of pyran-4-one and piperidin-4-one systems under solvent-free conditions. Relatively high yields of products are obtained from the reaction of ketones **1** with different aromatic and aliphatic aldehydes under the catalytic system of $TMSNMe_2$ and $MgBr_2.OEt_2$. Notably, formation of the undesired bis counterparts, as a major limitation of these reaction types, is minimized using the employed conditions.

1. Introduction

α,β-Unsaturated derivatives of ketones are very useful species in synthetic organic chemistry since they are the key substructure of many natural and biologically active compounds [1-4]. Moreover, these derivatives could be employed as useful precursors in other synthetic transformations [5-6]. Although various methods are available for the synthesis of these compounds [7-9], many of them involve multi-step procedures or demand the use of reactants or reagents which are not commercially available.

Claisen-Schmidt condensation is often a common pathway for the synthesis of α,β-unsaturated carbonyl systems via the reaction of aromatic aldehydes with ketones at their α position [10-14]. However, this approach requires the use of strong bases or acids and is often accompanied by competitive formation of the respective bis by-products. To overcome these drawbacks, recently, two independent groups reported new procedures catalyzed by N,N-dimethylammonium N',N'-dimethylcarbamate [15] and a pyrrolidine imide [16], respectively. These methods are based on catalytic cycles with proposed iminium transients for the conversion of reactants to the desired products.

In continuation of our investigations into aldol condensation reactions of various homo- and heterocyclic ketones [17-19], we have decided to apply our experience to the synthesis of the monoarylidene derivatives of such ketones [20,21]. On this basis, in this paper, we have reported the results achieved in pyran-4-one and piperidin-4-one heterocyclic systems (Scheme 1).

It is noteworthy that derivatives of the piperidinone system are considered as important six-membered nitrogen-containing heterocycles, due to possessing diverse biological properties, and which are widely found in natural resources [22-24]. The same case is applied to the pyran ring [25-28]. Consequently, new routes to access derivatives of these systems are nowadays of prominence in synthetic organic chemistry.

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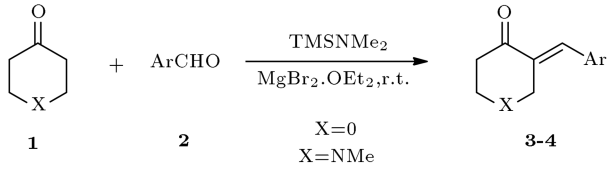


Scheme 1. General reaction for the synthesis of products **3-4**.

2. Experimental

2.1. General

Melting points are uncorrected. IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer. NMR spectra were obtained on a Bruker Ultra Shield^{TM} (500 MHz) as $CDCl_3$ solutions, using TMS as an internal standard reference. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. MS spectra were obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. TLC experiments were carried out on precoated silica gel plates using petroleum ether/EtOAc (4:1) as the eluent. A known procedure was used for the preparation of $MgBr_2OEt_2$ [29]. Solvents, $TMSNMe_2$, and other starting materials were purchased from commercial sources. Aldehydes were redistilled or recrystallized before being used. Products **3a** [20] are reported previously. All other products are new and their structures are determined based on their physical and spectroscopic specifications, as listed below.

2.2. Typical procedure

A mixture of an aldehyde (3.0 mmol), ketone **1** (3.0 mmol), $MgBr_2OEt_2$ (7 mol%, 54 mg), and $TMSNMe_2$ (176 mg, 237 μl, 1.5 mmol) was stirred at room temperature under an inert atmosphere for a given period of time. The progress of the reaction was monitored by TLC experiments. At the end, water (5 mL) was added to the mixture and the product was extracted with Et_2O (2 × 5 mL). The organic layer was dried over a column of Na_2SO_4. Evaporation of the solvent led to a residue, which was purified by column chromatography using silica gel and petroleum ether/EtOAc (4:1) as the eluent.

2.3. Spectral data of new products

(E)-3-(2-Fluorobenzylidene)dihydro-2H-pyran-4(3H)-one (3b). White solid was obtained in 75% yield. Mp 92-93°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68-2.70 (m, 2H), 4.06-4.09 (m, 2H), 4.70 (dd, J = 1.0, 1.5 Hz, 2H), 7.08-7.17 (m, 3H), 7.33-7.36 (m, 1H), 7.66 (d, J = 1.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl3) δ 40.4, 66.1, 69.0 (d, J = 4.0 Hz), 116.4 (d, J = 22.0 Hz), 122.7 (d, J = 13.5 Hz), 124.5 (d, J = 4.0 Hz), 128.8 (d, J = 4.0 Hz), 131.1 (d, J = 2.0 Hz), 131.7 (d, J = 8.5 Hz), 135.6, 161.3 (d, J = 250.0 Hz), 196.3 ppm; IR (neat) ν 1691, 1618, 1220 cm^{-1} ; MS (70 eV): m/z 206 (M$^+$), 178, 149, 133. Anal. Calcd for $C_{12}H_{11}FO_2$: C, 69.89, H, 5.38. Found: C 69.57; H, 5.46.

(E)-3-(4-Chlorobenzylidene)dihydro-2H-pyran-4(3H)-one (3c). White solid was obtained in 70% yield. Mp 106-107°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67-2.69 (m, 2H), 4.06-4.08 (m, 2H), 4.81 (s, 2H), 7.12 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.55 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.2, 65.9, 69.0, 129.4, 132.2, 133.2, 134.1, 135.1, 136.0, 196.3 ppm; IR (neat) ν 2861, 1683, 1596, 1235 cm^{-1}; MS (70 eV): m/z 222 (M$^+$), 166, 131, 115. Anal. Calcd for $C_{12}H_{11}Cl_{O2}$: C, 64.73; H, 4.98. Found: C, 64.34; H, 4.97.

(E)-Methyl 4-((4-oxodihydro-2H-pyran-3(4H)-ylidene)methyl)benzoate (3d). Yellow solid was obtained in 73% yield. Mp 121-122°C; ^{1}H NMR (500 MHz, CDCl3) δ 2.69-2.71 (m, 2H), 3.92 (s, 3H), 4.07-4.09 (m, 2H), 4.82 (d, J = 2.0 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.60 (d, J = Hz, 1H), 8.05 (d, J = 8.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, CDCl3) δ 40.2, 52.7, 65.9, 69.0, 130.2, 130.7, 130.9, 134.9, 135.4, 139.0, 166.8, 196.3 ppm; IR (neat) ν 1726, 1688, 1284 cm^{-1}; MS (70 eV): m/z 246 (M$^+$), 231, 187, 175, 131. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28, H, 5.73. Found: C 68.15; H, 5.78.

(E)-3-(4-Nitrobenzylidene)dihydro-2H-pyran-4(3H)-one (3e). Yellow solid was obtained in 76% yield. Mp 135-136°C; ^{1}H NMR (500 MHz, CDCl3) δ 2.71-2.74 (m, 2H), 4.09-4.12 (m, 2H), 4.82 (d, J = 2.0 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 2 Hz, 1H), 8.26 (d, J = 8.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.3, 65.9, 68.8, 124.3, 131.3, 133.3, 136.8, 141.0, 146.0, 196.0 ppm; IR (neat) ν 1687, 1509, 1347 cm^{-1}; MS (70 eV): m/z 233 (M$^+$), 216, 205, 160, 130. Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75. Found: C 61.96; H, 4.85.

(E)-3-(2-Methoxybenzylidene)dihydro-2H-pyran-4(3H)-one (3f). Yellow solid was obtained in 68% yield. Mp 102-103°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67-2.69 (m, 2H), 3.85 (s, 3H), 4.06-4.09 (m, 2H), 4.73 (d, J = 2.0 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 1.5, 7.5 Hz, 1H), 7.35 (ddd, J = 1.5, 7.5, 8.0 Hz, 1H), 7.85 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.4, 55.9, 66.2, 69.2, 111.2, 120.5, 123.7, 130.9, 131.5, 132.2, 133.6, 158.9, 196.9 ppm; IR (neat) ν 2948, 1689, 1459, 1255 cm^{-1}; MS (70 eV): m/z 218 (M$^+$), 187, 131, 119. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47. Found: C 71.11; H, 6.50.

(E)-3-(4-Methoxybenzylidene)dihydro-2H-pyran-4(3H)-one (3g). Yellow solid was obtained in

86% yield. Mp 75-76°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65-2.67 (m, 2H), 3.83 (s, 3H), 4.05-4.07 (m, 2H), 4.85 (d, J = 2.0 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.0, 55.8, 65.8, 69.3, 114.7, 127.5, 131.5, 133.1, 136.4, 161.1, 196.3 ppm; IR (neat) ν 1681, 1591, 1511 cm–^{1}; MS (70 eV): m/z 218 (M^+), 187, 162, 131, 119. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47. Found: C 71.21; H, 6.55.

(E)-3-(Furan-2-ylmethylene)dihydro-2H-pyran-4(3H)-one (3h). Yellow solid was obtained in 66% yield. Mp 89-90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.63-2.65 (m, 2H), 4.03-4.06 (m, 2H), 4.97 (d, J = 2.0 Hz, 2H), 6.52 (dd, J = 2.0, 3.5 Hz, 1H), 6.64 (d, J = 3.5 Hz, 1H), 7.38 (dd, J = 2.0 Hz, 1H), 7.58 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.8, 65.5, 69.1, 113.1, 118.4, 121.8, 129.8, 146.2, 151.9, 195.9 ppm; IR (neat) ν 1675, 1595, 1263 cm^{-1}; MS (70 eV): m/z 178 (M^+), 150, 122, 94. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41, H, 5.66. Found: C 66.89; H, 5.55.

(E)-3-(Thiophen-2-ylmethylene)dihydro-2H-pyran-4(3H)-one (3i). Yellow solid was obtained in 65% yield. Mp 116-117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.64-2.67 (m, 2H), 4.05-4.07 (m, 2H), 4.86 (d, J = 2.0 Hz, 2H), 7.15 (dd, J = 3.7, 5.0 Hz, 1H), 7.27 (d, J = 3.7 Hz, 1H), 7.58 (d, J = 5.0 Hz, 1H), 7.82 (dd, J = 2.0, 2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.7, 65.5, 68.9, 128.4, 128.7, 130.0, 131.9, 134.1, 138.2, 195.5 ppm; IR (neat) ν 2870, 1676, 1416 cm^{-1}; MS (70 eV): m/z 194 (M^+), 166, 138, 110. Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found. C, 61.78; H, 5.03.

(E)-3-(3-Methylbutylidene)dihydro-2H-pyran-4(3H)-one (3j). Yellow oil was obtained in 57% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, J = 6.5 Hz, 6H), 1.72-1.78 (m, 1H), 1.90 (dd, J = 7.0, 7.5 Hz, 2H), 2.53-2.56 (m, 2H), 3.95-3.98 (m, 2H), 4.51 (d, J = 1.0 Hz, 2H), 6.73-6.77(m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 28.6, 36.9, 39.9, 65.7, 67.7, 134.1, 139.4, 196.0 ppm; IR (neat) ν 2958, 1696, 1466 cm^{-1}; MS (70 eV): m/z 168 (M^+), 151, 112, 83.

(E)-1-Methyl-3-(2-methylbenzylidene) piperidin-4-one (4a). Yellow oil was obtained in 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.37 (s, 3H), 2.64-2.68 (m, 2H), 2.78-2.81 (m, 2H), 3.47 (d, J = 1.5 Hz, 2H), 7.05 (d, J = 7.5 Hz, 1H), 7.15-7.26 (m, 3H), 7.65 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 39.6, 46.4, 53.5, 57.6, 125.9, 129.2, 129.3, 130.7, 133.6, 134.3, 135.4, 138.5, 198.1 ppm; IR (neat) ν 2942, 1687, 1608 cm^{-1}; MS (70 eV): m/z 215 (M^+) 198, 186, 115. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96. Found. C, 78.22; H, 8.03.

(E)-1-Methyl-3-(2-methoxybenzylidene) piperidin-4-one (4b). Yellow oil was obtained in 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.68-2.69 (m, 2H), 2.84-2.86 (m, 2H), 3.59 (s, 2H), 3.82 (s, 3H), 6.89 (d, J = 7.5 Hz, 1H), 6.94 (dd, J =7.0, 7.5 Hz, 1H), 7.13 (d, J =7.0 Hz, 1H), 7.32 (dd, J = 7.0, 7.5 Hz, 1H), 7.79 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.3, 46.2, 53.3, 55.9, 57.8, 107.5, 111.2, 120.4, 124.2, 130.6, 131.1, 132.8, 158.9, 197.7 ppm; IR (neat) ν 2942, 1685, 1610 cm^{-1}; MS (70 eV): m/z 231 (M^+), 203, 188, 144, 124. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found. C, 72.88; H, 7.63.

(E)-1-Methyl-3-(3-methoxybenzylidene) piperidin-4-one (4c). Yellow oil was obtained in 71% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.47-2.67 (m, 2H), 2.82-2.88 (m, 2H), 3.67 (s, 2H), 3.80 (s, 3H), 6.86 (s, 1H), 6.88-6.97 (m, 2H), 7.30 (dd, J = 7.5, 8.0 Hz, 1H), 7.53 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.4, 46.5, 53.1, 55.7, 58,0, 115.0, 116.3, 123.1, 129.9, 133.5, 136.2, 136.5, 159.9, 197.9 ppm; IR (neat) ν 2940, 1686, 1599 cm^{-1}; MS (70 eV): m/z 231 (M^+), 202, 174, 145. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found. C, 72.97; H, 7.61.

(E)-3-(Furan-2-ylmethylene) -1-methylpiperidin-4-one (4d). Yellow oil was obtained in 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.54-2.57 (m, 2H), 2.70-2.72 (m, 2H), 3.70 (s, 2H), 6.43 (dd, J = 1.5, 1.5 Hz, 1H), 6.56 (d, J = 3.0 Hz, 1H), 7.26 (s, 1H), 7.50 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.2, 46.6, 52.7, 57.8, 112.9, 117.7, 122.2, 129.5, 145.7, 152.1, 197.3 ppm; IR (neat) ν 2944, 1681, 1598 cm^{-1}; MS (70 eV): m/z 191 (M^+),162, 134, 106. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found. C, 69.15; H, 6.72.

3. Results and discussion

We first optimized the conditions for the reaction of **1a** with benzaldehyde, as summarized in Table 1. The best results were obtained under solvent-free conditions and in the presence of $MgBr_2.OEt_2$ (7 mol%) and $TMSNMe_2$ (entry 1). Use of other amines, such as $NHEt_2$ (entry 2) and NEt_3 (entry 3), gave lower yields of **3a** and, therefore, formation of more quantities of the respective bis compound was observed. Omission of either the Lewis acid (entry 4) or the amine (entry 5) from the mixture led to the nearly complete recovery of the starting materials, proving that both additives are

Table 1. Optimization of the reaction conditions for the synthesis of **3a**.

Entry	Lewis acid	Amine[a]	Time (h)	Yield (%)[b]
1	$MgBr_2.OEt_2$	$TMSNMe_2$	6	73
2	$MgBr_2.OEt_2$	$NHEt_2$	6	35
3	$MgBr_2.OEt_2$	NEt_3	6	27
4	–	$TMSNMe_2$	12	< 5
5	$MgBr_2.OEt_2$	–	12	< 5
6	$Mg(ClO_4)_2$	$TMSNMe_2$	6	51
7	MgF_2	$TMSNMe_2$	6	39
8	$LiClO_4$	$TMSNMe_2$	6	44
9	LiBr	$TMSNMe_2$	6	41

[a]: 0.50 equivalents;

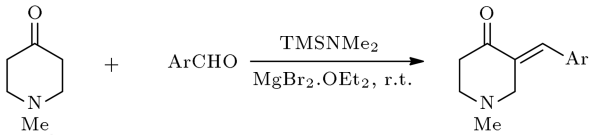
[b]: Isolated yields.

necessary for the progress of the reaction. Use of other Lewis acids could not also improve the yield (entries 6-9).

Under optimized conditions ($MgBr_2.OEt_2$/ $TMSNMe_2$), other aldehydes possessing electron withdrawing and electron releasing substituents behaved similarly to produce **3b-g** within 3-7 h (Table 2, entries 1-6). Use of heteroaromatic aldehydes (entries 7-8) further showed the generality of the procedure. A moderate yield was obtained for the same reaction with 3-methylbutanal **2j** (entry 9), an example of aliphatic aldehydes, which are also prone to self-condensation and usually give very low yields of the condensation product under aldol conditions.

Generally, the above reactions proceeded at ambient temperature and reached completion in short time periods, as indicated in the tables. ^{1}H NMR analysis of the reaction mixtures suggested that a single monoarylidene isomer with E geometry for the olefinic bond was formed in each case as the major product of the reaction. Comparison of ^{1}H NMR spectra shows that in the products possessing *ortho* substituents on the aldehyde residue, the H-2 protons shift slightly to lower fields. In particular, in the case of **3b**, the *ortho* fluorine atom causes the C-2 carbon signal to appear as a doublet in the ^{13}C NMR spectrum. Similarly, in the ^{1}H NMR spectrum, the C-2 protons, which are already coupled to the exocyclic olefinic proton, show an extra coupling with the fluorine atom, presumably due to a "through-space" hydrogen-fluorine interaction (Figure 1). These features provide solid evidence for the absolute stereochemistry of the exocyclic double bond.

To show the generality of the method, we then subjected ketone **1b** to the same conditions. Scheme 2 summarizes the results of the reactions of **1b** with



1b **2** **4**

Product	Ar	Time (h)	Yield (%)[a]
4a	$2\text{-}MeC_6H_4$	4	70
4b	$2\text{-}MeOC_6H_4$	5	68
4c	$3\text{-}MeOC_6H_4$	3	71
4d	$4\text{-}ClC_6H_4$	3	70
4e	2-furyl	4	73

[a]: Isolated yields.

Scheme 2. The reaction pathway for the synthesis of **4**.

various aldehydes, leading to formation of products **4a-e**, within 3-5 h time periods.

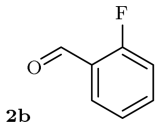
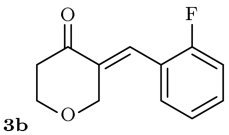
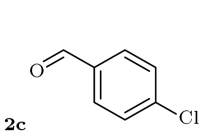
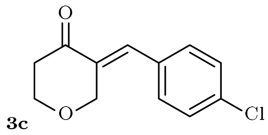
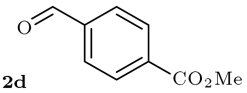
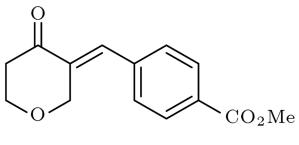
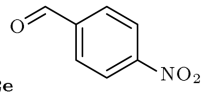
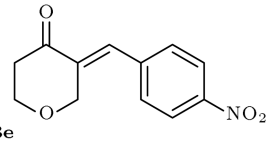
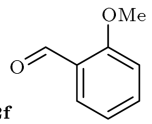
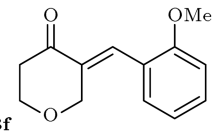
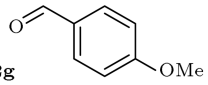
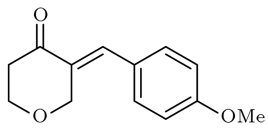
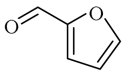
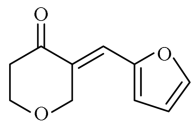
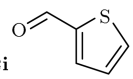
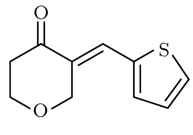
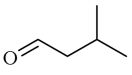
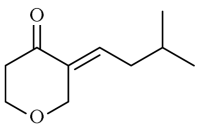
Based on these results, we propose a mechanism for the reaction (Figure 2). First, $TMSNMe_2$ facilitates conversion of the starting aldehyde into its respective in situ formed iminium salt. The trimethylsilanolate anion resulted from this conversion, then causes the enolization of the ketone **1** under the catalysis of $MgBr_2OEt_2$. At last, the reaction of the enol with the iminium ion gives the final product. This kind of mechanism for similar aldol condensation reactions involving iminium ion intermediates has precedence [15,16].

4. Conclusion

A significant advantage of the present method is the observed chemoselectivity, which leads to minimum formation of the unwanted bis byproducts. This must be due to the relatively mild conditions chosen for this reaction. In other words, formation of a bis byproduct has to go through enolization of **3**. This enolization is less feasible in the presence of a mild amine such as $TMSNMe_2$, because the protons of the starting ketone **1** are expected to be more acidic than those of **3** (four protons and a simple C=O in **1** vs. two protons and a conjugated C=O in **3**). Further, use of equimolar amounts of the aldehyde itself exhibits extensive formation of the undesired bis compounds.

In summary, a convenient protocol is presented for the efficient synthesis of monoarylidenes of two synthetically important heterocyclic ketones. The procedure takes place in one pot and involves mild reaction conditions. Moreover, the workup is easy and the use of expensive and commercially unavailable reagents is avoided, while equimolar quantities of the starting materials and trace amounts of the catalyst are employed. A search in the literature shows that there are only scattered reports available on the synthesis of a few derivatives of the title compounds [20,30-32] and this makes the present procedure a valuable addition to the related archive.

Table 2. Room-temperature $MgBr_2.OEt_2$ catalyzed synthesis of **3**.

Entry	Aldehyde	Product	Time (h)	Yield%[a]
1	 **2b**	 **3b**	3	75
2	 **2c**	 **3c**	6	70
3	 **2d**	 **3d**	4	73
4	 **2e**	 **3e**	3	76
5	 **2f**	 **3f**	7	68
6	 **2g**	 **3g**	6	86
7	 **2h**	 **3h**	4	66
8	 **2i**	 **3i**	4	65
9	 **2j**	 **3j**	7	57

[a]: Isolated yields.

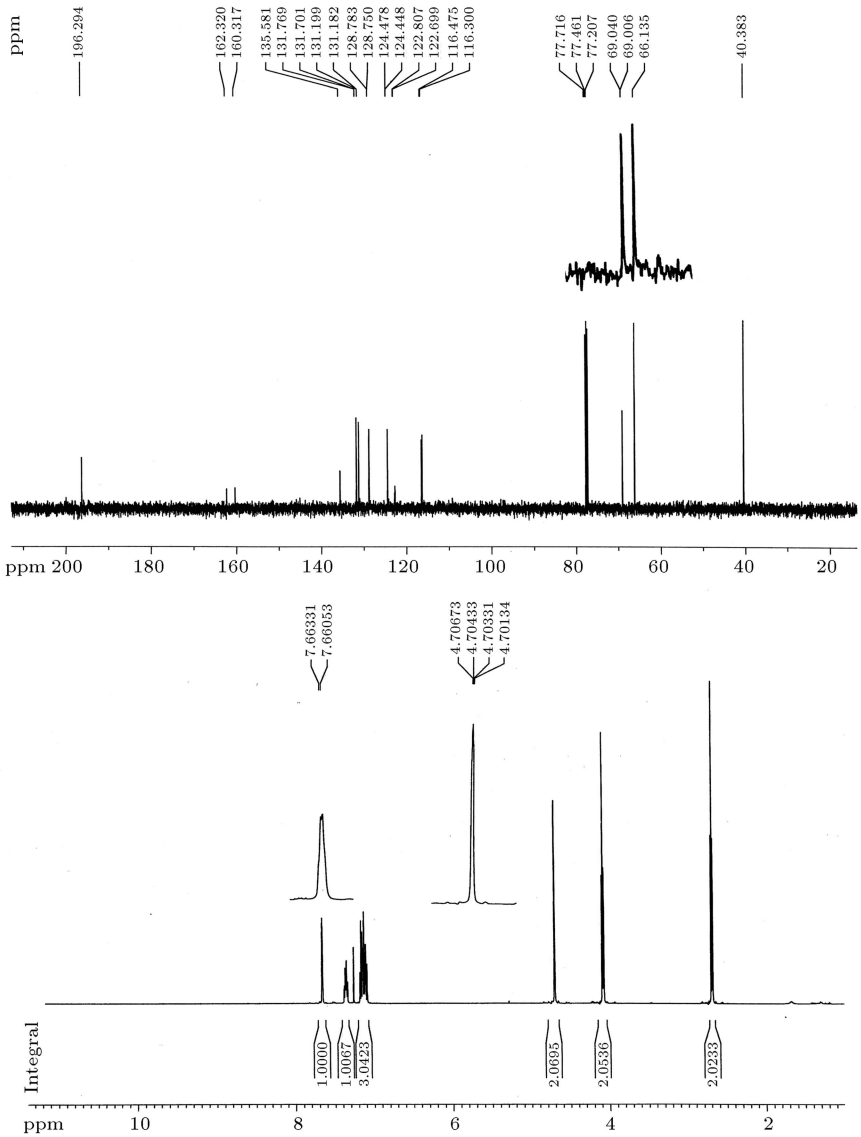


Figure 1. Elucidative "through-space" C-F (top) and H-F (bottom) couplings in **3b**.

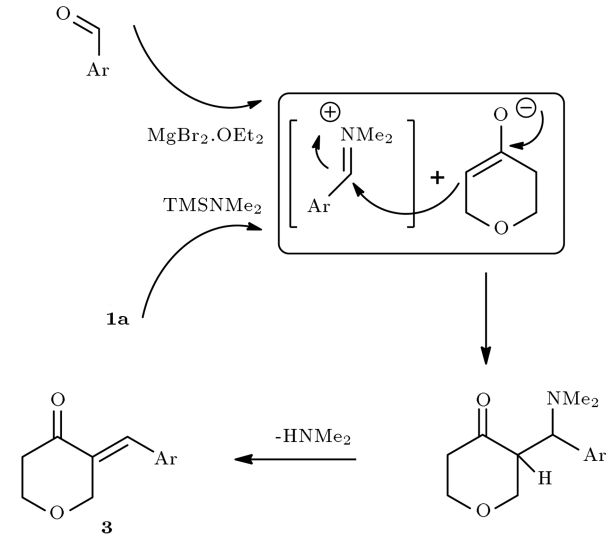


Figure 2. The suggested mechanism for the reaction.

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