A Highly Efficient Method for Solvent-Free Synthesis of Bis(arylmethylidene)piperidinones

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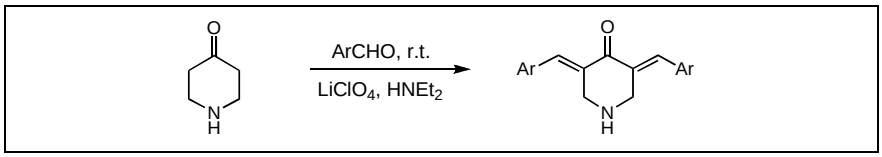

A remarkably efficient double crossed aldol condensation of piperidin-4-one with various aromatic aldehydes is described at room temperature in the presence of diethylamine and lithium perchlorate under solvent-free conditions. Excellent yields of 3,5-bis(arylmethylidene)piperidinones are achieved in a facile one-pot general procedure. Structure of the products is determined by spectroscopic methods and elemental analysis.

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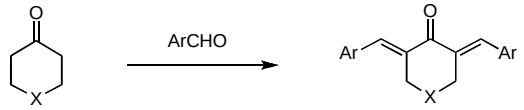
INTRODUCTION

Crossed aldol condensation of homocyclic ketones **1a**-**b** with aldehydes [1] is a useful method for the preparation of bis(arylmethylidene)cycloalkanones which are very important precursors in synthetic organic chemistry [2]. Many developments have been achieved in recent years to widen the synthetic scope of bisarylmethylidenes of homocyclic ketones [3] by microwave irradiation [4], ultrasound mediation [5], use of ionic liquids [6], and Lewis acid catalysis [7] (Scheme 1).

Scheme 1



1a: X=none
1b: X=CH_2
1c: X=S
1d: X=O
1e: X=NH

2a-g (X = NH)

In contrast, fewer investigations on similar heterocyclic counterparts have taken place [8]. Despite the importance of these compounds from biological and bioorganic points of view [9-10], they have been prepared *via* the condensation of **1c**-**e** with aromatic aldehydes under relatively harsh conditions and after long reaction time periods [9-11]. Our interest to develop the chemistry of heterocyclic systems [12] recently led us to report convenient procedures for the preparation of bisarylmethylidenes of thiopyranone **1c** and pyranone **1d** systems under lithium perchlorate ($LiClO_4$) [13] or magnesium bromide ethyl etherate [14] mediation. In continuation of these studies, we would like to report now a mild and general procedure for rapid synthesis of bisaryl-methylidenepipyridinones at room temperature.

The versatility of the present procedure is demonstrated by synthesizing several novel compounds. In the present article, a 1:2 mixture of $LiClO_4$ and diethylamine (Et_2NH) is employed to induce one-pot double condensation of ketone **1e** with aromatic aldehydes under solvent-free conditions.

RESULTS AND DISCUSSION

Table 1 highlights the elemental analysis and melting point data for products **2a**-**g** obtained from the condensation of various aromatic aldehydes with ketone **1e**. Initially, treatment of **1e** with benzaldehyde and Et_2NH in the presence of $LiClO_4$ facilitated the formation of the double crossed aldol condensation product of **2a** within few hours at room temperature. The reaction was found to be complete in less than 4 hours and the yield was 95%. The chemoselectivity of the reaction was evaluated by conducting parallel reactions using **1e** /benzaldehyde ratios of 1:1 and 1:2. In both cases the same product **2a** was formed in comparable quantities. Other control experiments were run to clarify the role of the reactants. A test reaction conducted in the absence of diethylamine gave no product. Omission of lithium perchlorate from the reaction medium also led to recovery of the majority of the starting materials. The generality of the method was shown by the synthesis of similar products (**2b**-**g**) using other aromatic aldehydes under the same conditions. All reactions were completed rapidly at room temperature. Under present conditions, all reactions proceed cleanly and no other products, which are normally observed under classical conditions, are detected. The present one-pot protocol involves mild reaction conditions, great efficiency, short reaction times, high product yields, and use of inexpensive commercially available materials. A mechanistic overview can be

Table 1

Elemental analysis and melting point data for products **2a**-**g**

	Compound	Composition	Elemental analysis Calculated (Found)	m.p. °C (Reported) [9]	Yield%
2a	Ar = C_6H_5	$C_{19}H_{17}NO$	C 82.88 H 6.22 N 5.09 (C 82.66H 6.35 N 4.99)	175-177 (177-178)	95
2b	Ar = 4-$CH_3OC_6H_4$	$C_{21}H_{21}NO_3$	C 75.20 H 6.31 N 4.18 (C 75.50 H 6.35 N 4. 12)	196-197 (210-211)	96
2c	Ar = 4-$CH_3C_6H_4$	$C_{21}H_{21}NO$	C 83.13 H 6.98 N 4.62 (C 83.15 H 7.07 N 4. 52)	180-181 (-)	96
2d	Ar = 4-ClC_6H_4	$C_{19}H_{15}Cl_2NO$	C 66.29 H 4.39 N 4.07 (C 66.66 H 4.29 N 4.30)	192-194 (201)	94
2e	Ar = 4-BrC_6H_4	$C_{19}H_{15}Br_2NO$	C 52.69 H 3.49 N 3.23 (C 52.90 H 3.57 N 3.35)	207-208 (-)	91
2f	Ar = 2,4,6-$(CH_3O)_3C_6H_2$	$C_{25}H_{29}NO_7$	C 65.92 H 6.42 N 3.07 (C 65.99 H 6.32 N 3.31)	198-199 (-)	93
2g	Ar = thiophen-2-yl	$C_{15}H_{13}NOS_2$	C 62.69 H 4.56 N 4.87 (C 62.76 H 4.42 N 4.52)	205-206 (-)	90

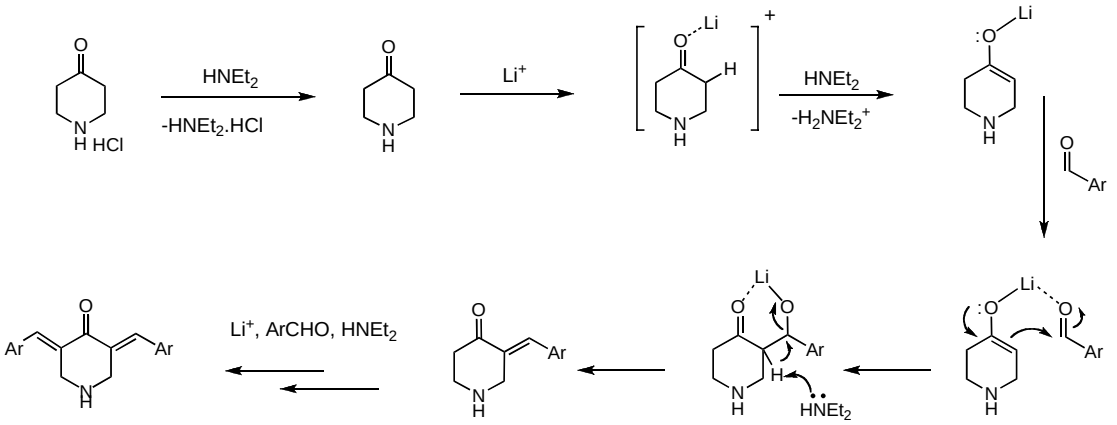


Figure 1. Mechanism of $LiClO_4$ condensation of **1e** with aldehydes.

concluded for the reaction of **1e** with aldehydes as depicted in the Figure 1.

Formation of the enolate in this mechanism is supported by the fact that both the Lewis acid and the amine are required for the reaction to proceed and in the absence of any of them no product is obtained. Such mechanism can also be concluded from similar aldol condensations previously conducted under Lewis acid/amine catalysis [14-15].

In conclusion, we have presented a novel, reliable, and efficient general synthetic protocol for the preparation of 3,5-bis(arylmethylidene)piperidinones at room temperature. The generality of this versatile reaction makes it an attractive addition to the present literature. We are currently exploring the feasibility of

Table 2

^{1}H NMR and IR Data for the Synthesized Compounds

Compound	^{1}H NMR (δ ppm)	IR (ν cm^{-1} KBr)
2a	($CDCl_3$) δ 1.68 (s, 1H, NH), 4.21 (s, 4H, H_2C-N-CH_2), 7.40-7.48 (m, 10H, Ar), 7.86 (s, 2H, CH=C)	3235 (NH), 1665 (C=C), 1593 (C=O)
2b	($CDCl_3$): δ 1.72 (s, 1H, NH), 3.90 (s, 6H, OCH_3), 4.19 (s, 4H, H_2C-N-CH_2), 6.98 (d, *J* = 9 Hz, 4H, Ar), 7.40 (d, *J* = 9 Hz, 4H, Ar), 7.81 (s, 2H, CH=C)	3242 (NH), 1667(C=C), 1509 (C=O)
2c	($CDCl_3$): δ 1.74 (s, 1H, NH), 2.43 (s, 6H, CH_3), 4.18 (s, 4H, H_2C-N-CH_2), 7.26 (d, *J* = 8 Hz, 4H, Ar), 7.32 (d, *J* = 8 Hz, 4H, Ar), 7.82 (s, 2H)	3289 (NH), 1657 (C=C), 1579 (C=O)
2d	($CDCl_3$) δ 1.77 (s, 1H, NH), 4.15 (s, 4H, H_2C-N-CH_2), 7.35 (d, *J* = 8.5 Hz, 4H, Ar), 7.43 (d, *J* = 8.5 Hz, 4H, Ar), 7.78 (s, 2H, CH=C)	3301 (NH), 1657 (C=C), 1584 (C=O)
2e	(DMSO-d_6) δ 3.40 (s, 1H, NH), 4.14 (s, 4H, H_2C-N-CH_2), 7.37 (d, *J* = 8 Hz, 4H, Ar), 7.60 (d, *J* = 8 Hz, 4H, Ar), 7.64 (s, 2H, CH=C)	3240 (NH), 1668 (C=C), 1585 (C=O)
2f	($CDCl_3$) δ 1.70 (s, 1H, NH), 3.43 (s, 4H, H_2C-N-CH_2), 3.74 (s, 12H, OCH_3), 3.88 (s, 6H, OCH_3), 6.13 (s, 4H, Ar), 7.70 (s, 2H, CH=C)	3350 (NH), 1650 (C=C), 1605 (C=O)
2g	($CDCl_3$) δ 1.85 (s, 1H, NH), 4.22 (s, 4H, H_2C-N-CH_2), 7.19 (dd, *J* = 4, 4.5 Hz, 2H), 7.38 (d, *J* = 4 Hz, 2H), 7.60 (d, *J* = 4.5 Hz, 2H), 7.98 (s, 2H, CH=C)	3291 (NH), 1647 (C=C), 1581 (C=O)

Table 3

^{13}C NMR Data for the Synthesized Compounds

Compound	δ ppm
2a	($CDCl_3$) δ 48.6 (NCH_2), 128.9, 129.5, 130.9, 135.4, 135.6, 136.4, 188.4 (C=O)
2b	($CDCl_3$): δ 48.6 (NCH_2), 55.8 (OCH_3), 114.5, 128.4, 132.9, 133.6, 136.1, 160.7, 188.3 (C=O)
2c	($CDCl_3$) δ 21.9 (CH_3), 48.6 (NCH_2), 129.7, 131.1, 132.9, 134.8, 136.3, 139.8, 188.4 (C=O)
2d	($CDCl_3$) δ 48.5 (NCH_2), 129.3, 132.1, 134.0, 135.1, 135.6, 135.7, 187.9 (C=O)
2f	($CDCl_3$) δ 54.2(NCH_2), 55.7 (OCH_3), 55.9 (OCH_3), 90.8, 107.2, 129.8, 134.9, 159.6, 162.4, 188.0 (C=O)
2g	($CDCl_3$) δ 48.2 (NCH_2), 127.5, 128.6, 131.3, 133.0, 133.6, 139.1, 187.0 (C=O)

constructing more complex compounds containing the piperidinones subunit by using products **2a**-**g**.

EXPERIMENTAL

Caution: Although we did not have any accident using $LiClO_4$, it is advisable to conduct the reactions of $LiClO_4$ containing mixtures in a fume hood behind a Lab. shield.

Melting points are uncorrected. IR spectra were recorded on a Bruker Vector-22 infrared spectrometer. NMR spectra were obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz) as $CDCl_3$ or DMSO-d_6 solutions using TMS as internal standard reference. Aldehydes were purified before use.

Typical procedure. Piperidin-4-one, **1e** (6.0 mmol, in the form of its hydrochloride monohydrate) was added to a mixture of the aldehyde (12.0 mmol), $LiClO_4$ (6.0 mmol), and Et_2NH (12.0 mmol). The mixture was stirred at room temperature and the process was monitored by TLC. After about 3-4 hours, the reactions were complete and the products precipitated out. The solid was washed by 0.5 *M* hydrochloric acid solution and brine. The precipitates were recrystalized by means of ethyl acetate. Isolated yields of the products were 90-96%. Spectral characterization data for compounds **2a**-**g** are given in the Table 2 and Table 3.

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REFERENCES

[1] Hathaway, B. A. *J. Chem. Educ*. **1987**, *64*, 367.

[2a] Deli, J. ; Lorand, T.; Szabo, D.; Foldesi, A. *Pharmazie* **1984**, *39*, 539; [b] Guilford, W. J.; Shaw, K. J.; Dallas, J. L.; Koovakkat, S.; Lee, W.; Liang, A.; Light, D. R.; McCarrick, M. A.; Whitlow, M.; Ye, B.; Morrissey, M. M. *J. Med. Chem.* **1999**, *42*, 5415; [c] Artico, M.; Di Santo, R.; Costi, R.; Novellino, E.; Greco, G.; Massa, S.; Tramintano, E.; Marongiu, M. E.; De Montis, A.; La Colla, P. *J. Med. Chem.* **1998**, *41*, 3948; [d] Jia, Z. C.; Quail, J. W.; Arora, V. K.; Dimmock, J. R. *Acta Cryst. Sect. C* **1989**, *45*, 1117; [e] Ogawa, M.; Ishi, Y.; Nakano, T.; Irifune, S. JP63,192,446 A2, 1988; *Chem. Abstr.***1989, 110,** 212211j; [f] Gangadhara, K. K. *Polymer* **1995**, *36*, 1903.

[3a] Zheng, M.; Wang, L.; Shao, J.; Zhong, Q. *Synth. Commun*. **1997**, *27*, 351; [b] Iranpoor, N.; Kazemi, E. *Tetrahedron* **1998**, *54*, 9475; [c] Nakano, T.; Migita, T. *Chem. Lett*. **1993**, 2157.

[4] Wang, J.; Kang, L.; Hu, Y.; Wei, B. *Synth. Commun*. **2002**, *32*, 1691.

[5] Li, J.; Yang, W.; Chen, G.; Li, T. *Synth. Commun*. **2003**, *33*, 2619.

[6a] Zheng, X.; Zhang, Y. *Synth. Commun*. **2003**, *33*, 161; [b] Hu, X.; Fan, X., Zhang, X.; Wang, J. *J. Chem. Res*. **2004**, 684; [c] Zhang, X.; Fan, X.; Niu, H. Wang, J. *Green Chemistry* **2003**, *5*, 267.

[7a] Abaee, M. S.; Mojtahedi, M. M.; Sharifi, R.; Zahedi, M. M.; Abbasi, H. Tabar-Heidar, K. *J. Iran. Chem. Soc*. **2006**, *3*, 293; [b] Wang, L.; Sheng, J.; Tian, H.; Han, J.; Fan, Z.; Qian, C. *Synthesis* **2004**, 3060; [c] Sabitha, G.; Reddy, K. K.; Reddy, K. B.; Yadav, J. S. *Synthesis* **2004**, 263; [c] Iranpoor, N.; Zeynizadeh, B.; Aghapour, A. *J. Chem. Res*. **1999**, 554; [d] Zhu, Y.; Pan, Y. *Chem. Lett*. **2004**, 668.

[8a] Rovnyak, G.; Shu, V.; Schwartz, J. *J. Heterocycl. Chem.* **1981**, *18*, 327; [b] Leonard, N. J.; Choudhury, D. *J. Am. Chem. Soc*. **1957**, *79*, 156.

[9] Dimmock, J. R. ; Padmanilayam, M. P.; Puthucode, R. N.; Nazarali, A. J.; Motaganahalli, N. L.; Zello, G. A.; Quail, J. W.; Oloo, E. O.; Kraatz, H. B.; Prisciak, J. S.; Allen, T. M.; Santos, C. L.; Balzarini, J.; Clercq, E. D.; Manavathu, E. K. *J. Med. Chem.* **2001**, *44*, 586.

[10] Costi, R.; Di Santo, R.; Artico, M.; Massa, S.; Regno, R.; Loddo, R.; La Colla, M.; Tramontano, E.; La Colla, P.; Pani, A. *Bioorg. Med. Chem.* **2004**, *12*, 199.

[11a] Al-Omar, M. A.; Youssef, K. M.; El-Sherbeny, M. A.; Awadalla, S. A. A.; El-Subbagh, H. I. *Arch. Pharm.* **2005**, *338*, 175; [b] Youssef, K. M.; El-Sherbeny, M. A.; El-Shafie, F. S.; Farag, H. A.; Awadalla, S. A. A. *Arch. Pharm.* **2004**, *337*, 42.

[12a] Ward, D. E. Abaee, M. S. *Org. Lett*. **2000**, *2*, 3937; [b] Ward, D. E.; Nixey, T. E.; Gai, Y.; Hrapchak, M. J.; Abaee, M. S. *Can. J. Chem.* **1996**, 1418; [c] Mojtahedi, M. M.; Jalali, M. R.; Bolourtchian, M. *Synth. Commun*. **2006**, *36*, 51; [d] Abaee, M. S.; Sharifi, R.; Borhani, S.; Heravi, M. M.; Motahari, H. *Heterocycl. Commun*. **2005**, *11*, 415; [e] Mojtahedi, M. M.; Abaee, M. S.; Jalali, M. R.; Bolourtchian, M. *Heterocycl. Commun*. **2006**, *12*, 225.

[13a] Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M. *Synlett* **2005**, 2317; [b] Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M.; Bolourtchian, M. *Synth. Commun*. **2006**, *36*, 199.

[14] Abaee, M. S.; Mojtahedi, M. M.; Zahedi, M. M. Sharifi. R. *Heteroatom Chem.* **2007**, *18*, 44.

[15] Arold, A.; Markert, M.; Mahrwald, R. *Synthesis* **2006**, 1099.