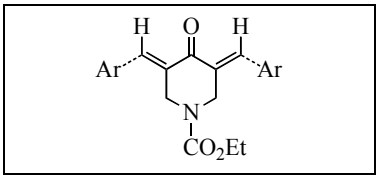
Iodine Catalyzed Synthesis of α,α'-Bis(Substituted Benzylidene)-1-Carbethoxy-4-Piperidone

Mohamed. A. Ameen* and Essam, Kh. Ahmed

Chemistry Department, Faculty of Science, El-Minia University, El-Minia, Egypt
E-mail: m_ameen10@yahoo.com
Received March 1, 2007



A facile and efficient method for the preparation of α,α'-bis(substituted benzylidene)-1-carbethoxy-4-piperidone is described using iodine as a catalyst in acetonitrile. The reaction proceeds rapidly at room temperature, giving high yields of products.

J. Heterocyclic Chem., **45**, 579 (2008).

INTRODUCTION

The α,α'-bis(substituted benzylidene)cycloalkanones are very important precursors to potentially bioactive pyrimidine derivatives [1], intermediates of agrochemical, pharmaceuticals, and perfumes [2], new organic materials for nonlinear optical applications [3], cytotoxic analogues [4] and the units of liquid-crystalline polymers [5]. In addition, these compounds undergo double 1,3-dipolar cycloaddition reaction [6] with azomethine ylides to give bis-spiropyrrolidines, which are often the central ring systems of numerous natural products [7].

Generally benzylidenecycloalkanones are prepared by cross-Aldol condensation of cycloalkanones with aldehydes in the presence of strong acids or bases. However, traditional acid- or base-catalyzed reactions often suffer from reverse and side reactions and therefore give low yields of products [8]. Cp_2TiPh_2 [9] and anhydrous $RuCl_3$ [10] are reported to give good yields of enone products, but require longer reaction times and high temperatures (120 °C) in sealed, ampoules and tubes, whereas Rh-porphyrin complex-catalyzed reactions reported to give 30% cross-Aldol product [11]. Microwave assisted syntheses [12] using KF/Al_2O_3 and BMPTO and several catalytic procedures [13] using different complexes of metal ions as catalysts have been reported. Solvent-free synthesis mediated by magnesium hydrogen sulfate [14] or $Yb(OTf)_3$ [15], is known for these compounds. However, this procedure requires longer reaction times (7 h) and heating temperature up to 60 °C.

Recently the preparation of products of the type of the title compounds has been reported [16] using $FeCl_3 \cdot 6H_2O$ as catalyst in an ionic liquid medium at 80 °C. Even though SmI_3 has been used to synthesize α,α'-bis(substituted benzylidene)cyclopentanones at room temperature, the required products can only be obtained by using cyclopentanone trimethylsilyl enol ethers as starting materials. Moreover, the temperature of the reaction has to be raised to 70–80 °C for the cyclohexanone analogue [17]. The first example in which cross-Aldol condensation of ketones with aldehydes was carried out at room temperature to give enones was reported by the use of iodotrimethylsilane (TMSI) [18].

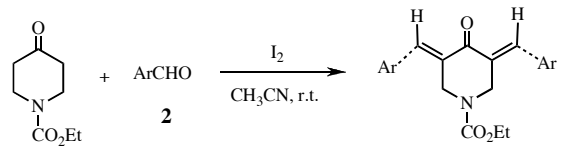
In this context, we now developed a mild and more efficient method for the synthesis of α,α'-bis(substituted benzylidene)-1-carbethoxy-4-piperidone at room temperature using CH_3CN as a solvent. While this work was progressing another research group [19] published the successful synthesis of analogues of our target compounds, containing a cyclopentanone unit, using iodine at RT.

RESULTS AND DISCUSSION

To the best of our knowledge, this is one of the few examples [18,19] in which cross-Aldol condensation of ketones with aldehydes, is carried out at room temperature to give enones. We found that CH_3CN is more effective solvent in terms of yields than other solvents tested such as $CHCl_3$, THF and EtOH. The minimum amount of iodine required to get maximum yields of the products is 39.5 mmol% with respect to the aldehydes (0.79 mmol of iodine is necessary for 2 mmol of an aldehyde along with one mmol of hetero ketone) (Scheme 1).

Firstly, the reaction of benzaldehyde (**2a**; 10 mmol) with 1-carbethoxy-4-piperidone (**1**; 5 mmol) was chosen as the model reaction to detect whether the use of iodine was efficient and to investigate the optimized conditions. The reaction was found to be complete at room temperature in 6 hours to give the desired product in 81% yield. In the absence of any catalyst, the product α,α'-dibenzylidene-1-carbethoxy-4-piperidone (**3a**) was obtained in a very low yield (9%) even after stirring for 2 days.

Scheme 1



1 **3**

Based on the results obtained above, we turned our attentions to apply the methodology to other derivatives. Several aromatic aldehydes were successfully reacted with the heterocyclic ketone and found that in all cases, the reactions proceeded rapidly at room temperature and complete conversion was observed with the amount of iodine tested to afford the corresponding α,α'-dibenzylidene-1-carbethoxy-4-piperidone derivatives in 81–96% yield. Thus the yields were excellent, including the heteroaromatic aldehyde thiophene-2-carbaldehyde. It seems that the effect of substituted groups on the aromatic aldehydes is not very strong; both the electron-donating [Me, MeO, $N(CH_3)_2$] and electron-withdrawing (NO_2, Cl) groups worked well, showing little distinction. The purifications of these compounds were easily performed by simple filtration and washing with ethanol.

It is important to note that the cross-Aldol reaction of aliphatic aldehydes with the ketone (Table 1, entry 8) also proceeded cleanly to give the corresponding di-Aldol product in good yield. Under the present conditions, all reactions were clean and free from any by-products, whereas, product mixtures were normally observed in classical reaction conditions [20]. The advantages of the present protocol are mild reaction conditions, greater efficiency, shorter reaction times, high yields of products, and use of inexpensive reagents.

It is important to point out that the reaction produces only one diastereomer as indicated in Scheme 1. The ^{1}H NMR proved the presence of olefinic-H proton affected by the carbonyl group (see the Experimental Section), since this proton appeared deshielded in the ^{1}H NMR spectra of **3a-j** at δ > 7.60. NOE experiments helped to confirm the proposed structure since irradiation of the olefinic proton in all substitutents causes strong enhancement to the methylene protons, whereas little effect was noted on the aryl protons.

In conclusion, we have achieved a general and efficient synthesis of α,α'-bis(substituted benzylidene)-1-carbethoxy-4-piperidone at room temperature using iodine as a catalyst. The scope and generality of the present method makes it an attractive addition to the existing methodologies in the literature.

EXPERIMENTAL

All the aldehydes, I_2 and acetonitrile were available commercially. 1-carbethoxy-4-piperidone was obtained from Merk. Melting points were determined on a Boetius melting point apparatus. Elemental analyses were performed on a Carlo Erba CHN-S Elemental Analyzer 1108. The ^{1}H NMR spectra were obtained using a Bruker AC 300 instrument (^{1}H: 200 MHz). The δ-values are given in ppm, and the internal standard was tetramethylsilane. Mass spectra were obtained on a Perkin-Elmer SCIEX API-300 spectrometer (by ion spray using heated nebulizer). The IR spectra were recorded on a Nicolet 250 FT-IR spectrophotometer on potassium bromide pellets.

General procedures for the synthesis of α,α'-bis-(substituted benzylidene)-1-carbethoxy-4-piperidone 3a-3j. A mixture of an aldehyde (2 mmol), 1-carbethoxy-4-piperidone (0.17 g, 1 mmol) and iodine (100 mg, 0.79 mmol) in CH_3CN (10 mL) was stirred for 6-12 h under N_2 atmosphere (the reaction was monitored by TLC analysis). After completion of the reaction the solvent was removed under vacuum and the residue was extracted with EtOAc. The EtOAc extract was washed with a solution of sodium thiosulfate (2 × 10 mL) and subsequently with water (3 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure yielded a solid, which was crystallized from EtOH or MeOH to afford the pure compound.

α,α'-Dibenzylidene-1-carbethoxy-4-piperidone (3a). This compound was obtained as pale yellow crystals (methyl alcohol), ir: 3075 (CH SP^2), 2978 (CH SP^3), 1700 (C=O ester), 1619 (C=O), 1583 (C=C) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$): δ 1.14 (t, 3H, $COOCH_2CH_3$), 4.11 (q, 2 H, $COOCH_2CH_3$), 4.82 (s, 4 H, H-2,6), 7.31-7.42 (m, 10 H, ArH), 7.86 (s, 2 H, 2 C=CH); ms: *m/z* 347 [M^+], 318, 274. *Anal.* Calcd. For $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.01; H, 6.02; N, 3.93.

Table 1

Synthesis of α,α'-bis(substituted benzylidene)-1-carbethoxy-4-piperidone catalyzed by molecular iodine.

Entry	Ar	Time (h)	Product	Color	Mp. (°C)	Yield (%)
1	C_6H_5	6	**3a**	Pale Yellow	152-153	81
2	*p*-ClC_6H_4	10	**3b**	Yellow	141-142	96
3	*p*-HOC_6H_4	8	**3c**	Orange	271-272	93
4	*p*-$MeOC_6H_4$	12	**3d**	Pale Yellow	162-163	92
5	*o*-$MeOC_6H_4$	12	**3e**	Yellow	117-118	93
6	*p*-$NO_2C_6H_4$	11	**3f**	Yellow	182-183	87
7	2-thienyl	9	**3g**	Orange	198-199	93
8	n-heptyl	7	**3h**	Pale Yellow	134-135	92
9	*p*-MeC_6H_4	6	**3i**	Yellow	167-168	96
10	*p*-$Me_2NC_6H_4$	9	**3j**	Orange	171-172	92

α,α'-Bis(*p*-chlorobenzylidene)-1-carbethoxy-4-piperidone (3b). This compound was obtained as yellow crystals (ethyl alcohol), ir: 3084, 2962, 1705, 1629, 1578 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 1.12 (t, 3 H, $COOCH_2CH_3$), 4.06 (q, 2 H, $COOCH_2CH_3$), 4.76 (s, 4 H, H-2,6), 7.32-7.39 (m, 8 H, ArH), 7.72 (s, 2 H, 2 C=CH); ms: m/z 415 [M^+], 386, 342, 151, 115. *Anal*. Calcd for $C_{22}H_{19}Cl_2NO_3$: C, 63.47; H, 4.60; Cl, 17.03; N, 3.36. Found: C, 63.36; H, 4.51; Cl, 16.92; N, 3.24.

α,α'-Bis(*p*-hydroxybenzylidene)-1-carbethoxy-4-piperidone (3c). This compound was obtained as orange crystals (ethyl alcohol), ir: 3500, 3070, 2985, 1708, 1623, 1586 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 1.14 (t, 3 H, $COOCH_2CH_3$), 4.10 (q, 2 H, $COOCH_2CH_3$), 4.77 (s, 4 H, H-2,6), 7.28-7.41 (m, 8 H, ArH), 7.84 (s, 2 H, 2 C=CH); ms: m/z 379 [M^+], 350, 306. *Anal*. Calcd for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.58; N, 3.69. Found: C, 69.48; H, 5.39; N, 3.42.

α,α'-Bis(*p*-methoxybenzylidene)-1-carbethoxy-4-piperidone (3d). This compound was obtained as pale yellow crystals (methyl alcohol), ir: 3082, 2987, 1706, 1634, 1575 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 1.09 (t, 3 H, $COOCH_2CH_3$), 3.80 (s, 6 H, 2 OCH_3). 4.13 (q, 2 H, $COOCH_2CH_3$), 4.69 (s, 4 H, H-2,6), 7.33-7.46 (m, 8 H, ArH), 7.81 (s, 2 H, 2 C=CH); ms: m/z 407 [M^+], 378, 334. *Anal*. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18, N, 3.44. Found: C, 70.64; H, 6.02, N, 3.31.

α,α'-Bis(*o*-methoxybenzylidene)-1-carbethoxy-4-piperidone (3e). This compound was obtained as yellow crystals (methyl alcohol), ir: 3070, 2985, 1710, 1642, 1574 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 1.11 (t, 3 H, $COOCH_2CH_3$), 3.71 (s, 6 H, 2 OCH_3). 4.12 (q, 2 H, $COOCH_2CH_3$), 4.72 (s, 4 H, H-2,6), 7.29-7.56 (m, 8 H, ArH), 7.85 (s, 2 H, 2 C=CH); ms: m/z 407 [M^+], 378, 334. *Anal*. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18, N, 3.44. Found: C, 70.63; H, 6.01, N, 3.31.

α,α'-Bis(*p*-nitrobenzylidene)-1-carbethoxy-4-piperidone (3f). This compound was obtained as yellow crystals (ethyl alcohol), ir: 3090, 2965, 1706, 1629, 1570 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 1.12 (t, 3 H, $COOCH_2CH_3$), 4.06 (q, 2 H, $COOCH_2CH_3$), 4.74 (s, 4 H, H-2,6), 7.30-7.39 (m, 8 H, ArH), 7.69 (s, 2 H, 2 C=CH); ms: m/z 437 [M^+], 408, 364.. *Anal*. Calcd for $C_{22}H_{19}N_3O_7$ C, 60.41; H, 4.38; N, 9.61. Found: C, 60.28; H, 4.21; N, 9.41.

α,α'-Bis(thiophene-2-ylmethylene)-1-carbethoxy-4-piperidone (3g). This compound was obtained as orange crystals (methyl alcohol), ir: 3120, 2990, 1711, 1635, 1575 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 1.11 (t, 3 H, $COOCH_2CH_3$), 4.08 (q, 2 H, $COOCH_2CH_3$), 4.75 (s, 4 H, H-2,6), 7.16 (t, J = 3.7 Hz, 2 H), 7.39 (d, J = 2.5 Hz, 2 H), 7.54 (d, J = 4.6 Hz, 2 H), 7.79 (s, 2 H, 2 C=CH). ms: m/z 359 [M^+], 330, 386. *Anal*. Calcd for $C_{18}H_{17}NO_3S_2$: C, 60.14; H, 4.77; N, 3.90. Found: C, 60.01; H, 4.62; N, 3.73.

α,α'-Dioctylidine-1-carbethoxy-4-piperidone (3h). This compound was obtained as pale yellow crystals (ethyl alcohol), ir: 2970, 1708, 1639, 1575 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 1.08 (br. t, 6 H, 2 CH_3), 1.11 (t, 3 H, $COOCH_2CH_3$), 1.14-1.60 (m, 20 H, 10 CH_2), 4.06 (q, 2 H, $COOCH_2CH_3$), 4.74 (s, 4 H, H-2,6), 7.60 (t, 2 H, J = 8 Hz, 2 C=CH); ms: m/z 363 [M^+], 334, 290. *Anal*. Calcd for $C_{22}H_{37}NO_3$: C, 72.69; H, 10.26; N, 3.85. Found: C, 72.52; H, 10.11; N, 3.71.

α,α'-Bis(*p*-methylbenzylidene)-1-carbethoxy-4-piperidone (3i). This compound was obtained as yellow crystals (ethyl alcohol), ir: 3085, 2985, 1702, 1634, 1565 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$)::δ 1.09 (t, 3 H, $COOCH_2CH_3$), 2.39 (s, 6 H, 2 CH_3). 4.12 (q, 2 H, $COOCH_2CH_3$), 4.67 (s, 4 H, H-2,6), 7.30-7.48 (m, 8 H, ArH), 7.83 (s, 2 H, 2 C=CH); ms: m/z 375 [M^+], 346, 302. *Anal*. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.61; H, 6.55; N, 3.59.

α,α'-Bis(*p*-*N*,*N*-dimethylaminobenzylidene)-1-carbethoxy-4-piperidone (3j). This compound was obtained as orange crystals (methyl alcohol), ir: 3082, 2987, 1706, 1634, 1575 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$): δ 1.11 (t, 3 H, $COOCH_2CH_3$), 3.04 (s, 12 H, 4 NCH_3). 4.14 (q, 2 H, $COOCH_2CH_3$), 4.71 (s, 4 H, H-2,6), 7.33-7.48 (m, 8 H, ArH), 7.78 (s, 2 H, 2 C=CH); ms: m/z 433 [M^+], 404, 360. *Anal*. Calcd for $C_{26}H_{31}N_3O_3$ (433.56): C, 72.03; H, 7.21; N, 9.69. Found: C, 71.87; H, 7.03; N, 9.51.

REFERENCES AND NOTES

[1] Deli, J.; Lorand, T.; Szabo, D.; Foldesi, A. *Pharmaz*. **1984**, *39*, 539.

[2] Ogawa, M.; Ishii, Y.; Nakano, T..; Irifune, S. inventors; Jpn. Kohai Tokkyo JP 63192446 2. OgawaMIshiiYNakano-TIrifuneSJpn. Kohai Tokkyo JP63192446 A21988; *Chem. Abstr*. *Chem. Abstr*. 19881988, 63 63, 238034.

[3] Kawamata, J.; Inoue, K.; Inabe, T.; Kiguchi, M.; Kato, M.; Taniguchi, Y. *Chem. Phys. Lett*. **1996**, *249*, 29.

[4] Dimmock, J. R.; Padmanilayam, M. P.; Zello, G. A.; Nienaber, K. H.; Allen, T. M.; Santos, C. L.; De Clercq, E.; Balzarini, J.; Manavathu, E. K.; Stables, J. P. *Eur. J. Med. Chem*. **2003**, *38*, 169.

[5] Kaushal, K. *Polym*. **1995**, *36*, 1903.

[6] Raj, A.; Raghunathan, R. *Synth. Commun*. **2002**, *32*, 3295.

[7] Otohiko, T.; Kanemasa, S.; Ohen, M.; Yorozu, K. *Bull. Chem. Soc*. Jpn. **1987**, *60*, 4067.

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

[9] Nakano, T.; Migita, T. *Chem. Lett*. **1993**, *12*, 2157.

[10] Iranpoor, N.; Kazemi, F. *Tetrahed*. **1998**, *54*, 9475.

[11] Aoyama, Y.; Tanaka, Y.; Yoshida, T.; Toi, H.; Ogoshi, H. *J. Organometal. Chem*. **1987**, *329*, 251.

[12] (a) Yadav, J. S.; Reddy, B. V. S.; Nagaraju, A.; Sarma, J. A. R. P. *Synth. Commun*. **1996**, *26*, 503. (b) Wang, J. X.; Kang, L.; Hu, Y.; Wei, B. G. *Synth. Commun*. **1996**, *26*, 503. (c) Zheng, M.; Wang, L.; Shao, J.; Zhong, Q. *Synth. Commun*. **1997**, *27*, 351.

[13] Irie, K.; Watanabe, K. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 1366.

[14] Zhang, X.; Fan, X.; Niu, H.; Wang, J. *Green Chem*. **2003**, *5*, 267.

[15] Limin Wang, Jia Sheng, He Tian, Jianwei Han, Zhaoyu Fan, Changtao Qian, *Synthesis* **2004**, 3060-3064

[16] Salehi, P.; Khodaei, M. M.; Zolfigol, M. A.; Keyvan, A. *Monatsh. Chem*. **2002**, *133*, 1291.

[17] Bao, W.; Zhang, Y.; Ying, T. *Synth. Commun*. **1996**, *26*, 503.

[18] Gowravaram Sabitha, G. S.; Kiran Kumar Reddy, K.; Bhaska Reddy, J. S. Yadav, *Synth*. **2004**, 263-266

[19] Das, B.; Thiropathi, P.; Mahender, I.; Reddy, K. R. *J. of Molecular Catalysis A: Chemic,* **2006**, *247*, 182.

[20] Nekano, T.; Irifune, S.; Vmano, S.; Inada, A.; Ishii, Y.; Ogawa, M. J. Org. Chem. **1987**, *52*, 2239.