Monatsh Chem
DOI 10.1007/s00706-012-0811-8

ORIGINAL PAPER

Retro-aldol reactions in micellar media

Elena V. Vashchenko · Irina V. Knyazeva · Alexander I. Krivoshey · Valerii V. Vashchenko

Received: 19 December 2011 / Accepted: 25 June 2012

Abstract Convenient methods for retro-aldol reactions of α, β-unsaturated ketones in micellar media under acidic or basic conditions are proposed that enable obtaining optically pure (3*R*)-methylcyclohexanone and (1*R*,4*R*)-4-methylmenthone in high yields.

Keywords Retro reactions · Ketones · Micelles · Surfactants

Introduction

Aldol and crotonic condensation reactions are powerful organic synthesis tools for the formation of a carbon–carbon bond [1, 2]. Although the reverse process, the retro-aldol reaction, is less widespread, it nevertheless plays an important role in solving of certain synthetic tasks. Thus, retro-aldol reaction is a simple and useful method for obtaining (3*R*)-methylcyclohexanone from naturally occurring (+)-pulegone [3–6]. Moreover, the retro-aldol reaction is used in the total synthesis of steroids when introducing an angular methyl group [7, 8], for obtaining optically pure 4-methylmentone [9–11], and in the asymmetric synthesis of optically pure 2-phenylethanols [12].

The lack of a general and effective method for the retro-aldol reaction is often a restriction for its more widespread use in organic synthesis. For example, in the synthesis of steroids and some model compounds, using the benzylidene group as both a blocking and activating group has been proposed [7, 13–15]. However, this method has not found widespread use because of the difficulties of the removal of a benzylidene moiety. Thus, in the synthesis of 2-methyldecal-1-one, the benzylidene group has been removed in several steps including chlorination followed by treatment with sodium ethylate and aqueous alkali [7, 8].

Obviously, the retro-aldol reaction requires media with high water content (either under acidic or basic catalysis conditions), whereas the solubility of arylidene derivatives in such media is extremely low, and this causes low reaction rates and thus leads to low yields of the products. Generally, the use of surfactants, which means carrying out the reaction in micellar media, could result in substantial enhancement of the process performance [16, 17]. However, only a few examples of the use of such an approach for the retro-aldolization of pulegone and cinnamaldehyde are known at this time [18, 19].

In this work, convenient methods for retro-aldol reactions in micellar media under either acidic or basic conditions are proposed. These methods are especially useful for the ketones possessing steam volatility. (3*R*)-Methylcyclohexanone and (1*R*,4*R*)-4-methylmenthone have been taken as examples to obtain optically pure target compounds in high yields.

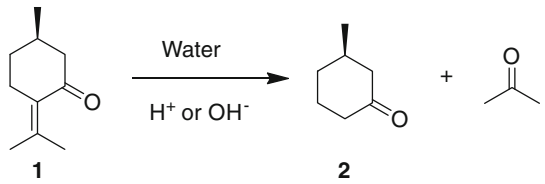
Results and discussion

Retro-aldol reaction in micellar medium under acidic conditions. Synthesis of (3R)-methylcyclohexanone from (+)-pulegone

The most practical method for the synthesis of optically pure (3*R*)-methylcyclohexanone (**2**) is the retro-aldolization of

E. V. Vashchenko · I. V. Knyazeva · A. I. Krivoshey · V. V. Vashchenko (✉)
SSI "STC" "Institute for Single Crystals" of NAS of the Ukraine, 60 Lenin ave., Kharkov 61001, Ukraine
e-mail: vvv6517@mail.ru; valeravv@isc.kharkov.com

Published online: 02 August 2012



Scheme 1

naturally occurring (+)-pulegone (**1**), which is the main component of pennyroyal oil (Scheme 1).

Conventionally, this reaction is carried out under acidic conditions by heating (+)-pulegone in hydrochloric acid [3–5] (Table 1, entry 1) or in diluted aqueous sulfuric acid [6] (Table 1, entry 2). The reaction is accelerated by distillation of the forming acetone followed by steam distillation of the main product **2**, which shifts the equilibrium of the reaction favorably. Nevertheless, even in the case of distillation of the products, the reaction time is 7–8 h, and the yield of the target compound **2** does not exceed 70 % (Table 1, entry 1). It seems that these results are caused by the low solubility of (+)-pulegone in the aqueous medium. In turn, the low solubility of **1** causes a relatively low rate of the main reaction and the accumulation of by-products of acid-catalyzed side processes in the reaction mixture with time. In order to solubilize compound **1** in the reaction mixture, the industrial method for carrying out the reaction under basic conditions in a micellar medium with the use of sodium dodecylsulfate (SDS) as the surfactant has been proposed [18] (Table 1, entry 3). The use of this method enables obtaining the target compound in better yields up to 73 %. However, the reaction time is much longer (up to 6 days) in comparison to acidic conditions. The need to maintain a desired pH of the reaction mixture by addition of fresh NaOH portions should also be considered as a disadvantage of this method.

In order to overcome the aforementioned problems, we combined the advantages of the acid-catalyzed process providing a high reaction rate with the ability of micellar media to solubilize the starting material, which also enables a more rapid reaction. The well-known cationic surfactant cetylpyridinium chloride (CPC) was used to obtain the micellar medium. Retro-aldolization of **1** in diluted aqueous H_2SO_4 in the presence of CPC with fractional distillation of the forming acetone followed by steam distillation of the target compound **2** allows a shortening of the reaction time to 2 h and an improvement in the yield of pure **2** up to 85 % (Table 1, entry 4). Moreover, it should be noted that (3*R*)-methylcyclohexanone (**2**) steam distilled in such a way from the reaction mixture possesses a rather high purity (more than 95 % according to GC; Table 1, entry 4); thus, it can be used in further transformations without additional purification.

Retro-aldol reaction in micellar medium under basic conditions. Synthesis of (1R,4R)-4-methylmenthone from (1R,4R)-2-benzylidene-p-menthane-3-ones

It has been shown previously [9–11] that the synthesis of optically pure (1*R*,4*R*)-4-methylmenthone can be achieved by the reaction sequence shown in Scheme 2.

Crotonic condensation of menthone (**3**) with aromatic aldehydes **4a–4c** gives corresponding arylidene derivatives **5a–5c** in 78–84 % yield [20]. The following methylation of compounds **5a–5c** with MeI/*tert*-BuOK occurs with high stereoselectivity to give the corresponding (1*R*,4*R*)-2-arylidene-4-methyl-*p*-menthan-3-ones **6a–6c** [9–11]. We were confronted with difficulties when carrying out the last step of removal of the arylidene group. In contrast to their non-methylated analogues **5a–5c**, the methylated arylidenementhanones **6a–6c** appear to be very stable in aqueous alkaline and alcoholic aqueous alkaline media, and undergo only slow retro-aldolization even with long-term heating (Table 2, entry 1). Sequential treatment of **6a–6c** with an alcoholic aqueous HCl solution followed by an alkaline solution results in formation of (1*R*,4*R*)-4-methylmenthone (**7**) in a very low yield (Table 2, entry 2), which is probably caused by acid-catalyzed rearrangement of **6a–6c** accompanied with by migration of the arylidene double bond into the ring [1, 21, 22]. The rearrangement is also believed to be the main reason for the formation of the

Table 1 The retro-aldolization of (+)-pulegone (**1**)

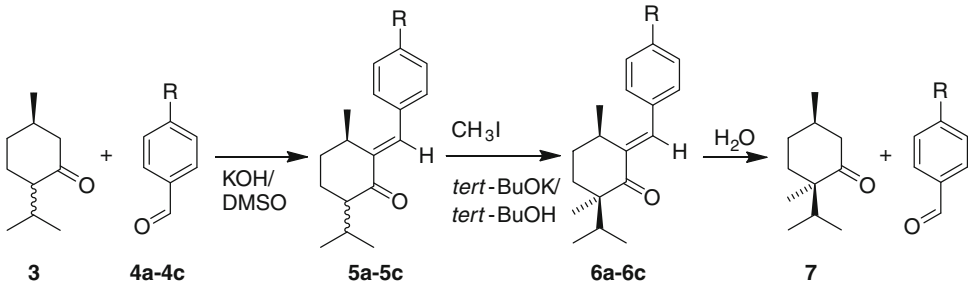
Entry	Catalyst/solvent	Surfactant	Reaction time[a]/h	Yield/%	Purity (GC)/%	Ref.
1	HCl/H_2O	None	7–8	62–70	n/a	[3–5]
2	H_2SO_4/H_2O	None	15	65	n/a	[6]
3	$NaOH/H_2O$	SDS	~144[b]	73	n/a	[18]
4[c]	H_2SO_4/H_2O	CPC	2	85 (91)	98 (>95)	

[a] The reaction time is considered to be the time required for the complete acetone distillation

[b] Restricted capacity and performance of a fractionating column should be taken into account in this case of large amounts of materials at the industrial scale

[c] The yield and purity of (3*R*)-methylcyclohexanone (**2**) steam distilled directly from the reaction mixture are given in brackets

Scheme 2



R = H **(a)**, OMe **(b)**, Br **(c)**

Table 2 Synthesis of (1*R*,4*R*)-4-methylmenthone (**7**) from (1*R*,4*R*)-2-arylidene-4-methyl-*p*-menthan-3-ones **6a–6c**

Entry	Starting material	Reaction conditions	Reaction time/h	Yield/%
1	**6c**	KOH, EtOH	~168	32 [9]
2	**6c**	1. HCl, EtOH	8	5 [9]
		2. KOH, EtOH	72	
3	**6a**	H_2SO_4, CPC	72	Traces[a]
4	**6a**	1. NaOH, SDS	24	7[a, b]
5	**6a**	1. NaOH, DMSO, SDS	8	46[c]
		2. $KMnO_4$, Na_2CO_3, H_2O		
6	**6b**	1. NaOH, DMSO, SDS	8	96[d] (67[c])
		2. $KMnO_4$, Na_2CO_3, H_2O		

[a] According to GC-MS

[b] The yield is calculated from compound **6a**

[c] The yield is calculated from starting menthone **3**

[d] The yield is calculated from compound **6b**

target compound **7** only in trace amounts (Table 2, entry 3) by carrying out the reaction similarly to the retro-aldolization of pulegone described and discussed above (Table 1, entries 6, 7).

Addition of the anionic surfactant SDS to the aqueous alkaline solution (similarly to the description in [18]) also does not improve the yield considerably (Table 2, entry 4). Addition of a small amount of isopropyl alcohol acting as anti-foaming agent also did not affect the yield of the target compound.

Based on the assumption that addition of DMSO to the reaction mixture will promote not only direct condensation (as described in [20]) but also the reverse retro-aldolization process, we used a 6:8:1 mixture of water/DMSO/*i*-PrOH (v/v) along with SDS as the reaction medium. Indeed, combined addition of DMSO and SDS has a synergic effect that enables the completion of the reaction in 7–8 h (Table 2, entry 5), and the products of the reaction (**4a** and **7**) are steam distilled from the reaction mixture. To separate **4a** from the target compound **7**, we used transformation of **4a** into a non-volatile compound, i.e., base-catalyzed oxidation of **4a** to the corresponding benzoic acid with potassium permanganate. The target 4-methylmenthone (**7**) is stable at such conditions, and it can be steam distilled from the reaction mixture after short-term heating. According to GC-MS, the product thus obtained is almost individual. However, taking into account that intermediate 2-arylidene derivatives **5a** and **6a** are oils and thus they were used without additional purification, the yield of **7** (46 %) is given per starting menthone **3**.

It is worth mentioning that it is more convenient to use 4-methoxybenzylidene derivative **6b** instead of **6a** for the synthesis of **7** since compound **6b** possesses a higher melting point and can be easily separated by crystallization from both unreacted menthone (**3**) and products of its alkylation (in contrast to the arylidene derivatives **5**, alkylation of menthone occurs non-selectively [9–11]; Scheme 2, second step), which could decrease the optical purity of the target compound **7**. Moreover, anisaldehyde (**4b**) appears to be much less steam volatile than benzaldehyde (**4a**); thus, it can be separated much more easily. By using compound **6b** for the retro-aldolization reaction (1*R*,4*R*)-4-methylmenthone (**7**) is obtained with an almost quantitative yield (Table 2, entry 6). The total yield of three steps is 67 % per starting menthone (**3**).

In conclusion, carrying out the retro-aldol reaction under acidic conditions in the micellar medium of the cationic surfactant CPC enables obtaining optically pure (3*R*)-methylcyclohexanone with a relatively short reaction time in high yield and purity. In the case of α,β-unsaturated ketones, e.g., arylidene derivatives of (1*R*,4*R*)-4-methylmenthone, which are prone to acid-catalyzed rearrangements, basic reaction conditions in the micellar medium of the anionic surfactant SDS in combination with the addition of a polar aprotic solvent (DMSO) are preferable. In the last case, separation of the ketone from the accompanying aromatic aldehyde can be effectively achieved by oxidation of the aldehyde in mild conditions. In both cases, steam volatility of the target ketone simplifies their isolation.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury VX-200 (200 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 using the signal of residual protons of undeuterated solvent as the internal standard [23]. Mass spectra were recorded on a Varian 1200 L GC-MS instrument either in GC-MS mode or with the use of the direct exposure probe (DEP) method with EI at 70 eV. Elemental analyses were performed with an EA-3000 analyser (Eurovector, Italy). IR spectra were recorded on a FT-IR "Spectrum One" instrument (Italy); samples were placed between ZnSe plates. TLC was performed using TLC aluminum sheet silica gel 60 F_{254} (Merck), and detection was done in an iodine chamber. (+)-Pulegone (**1**), (–)-menthone (**3**), and aromatic aldehydes **4a–4c** are commercially available. Arylidene-*p*-menthan-3-ones **5a–5c** were obtained according to [20]; (1*R*,4*R*)-2-arylidene-4-methyl-*p*-menthan-3-ones **6a–6c** were synthesized from substances **5a–5c** as described in [9–11].

(3R)-Methylcyclohexanone (**2**)

(+)-Pulegone (58.7 g, available from Acros Organics, purity 92 %, 54.0 g of pure pulegone), 250 cm^3 water, 60 cm^3 sulfuric acid, and 1 g cetylpyridinium chloride (CPC) were mixed in a round-bottom flask equipped with a distillation column (50 × 2 cm, packed with stainless steel helices and a variable take off head), and gently heated with stirring. The acetone fraction (b.p.: 56–60 °C) was slowly distilled off for approximately 2 h. Then the distillation column was substituted with a dropping funnel, the reaction mixture was refluxed, and steam distilled (3*R*)-methylcyclohexanone together with water was collected in the funnel. The separated water layer was returned into the reaction mixture. When steam distillation had finished (in approximately 2 h), the mixture was cooled, and the organic layer was collected and diluted with dichloromethane. The resultant solution was dried with $CaCl_2$, filtered, and evaporated to give the crude product (36.2 g, 91 %, purity 95.4 % according to GC–MS) as a slightly yellow oil. Distillation under atmospheric pressure gives pure (3*R*)-methylcyclohexanone (33.8 g, 85 % yield) as a colorless oil. B.p.: 167.0–167.5 °C; purity 97.8 % (according to GC–MS); $[\alpha]_D^{20} = +12.5°$ cm^2 g^{-1} (neat) (Ref. [24]: $+12.01°$ cm^2 g^{-1}). The ^{1}H NMR spectrum of compound **2** was found to agree with the reported data [25].

(1R,4R)-4-Methylmenthan-3-one (**7**)

In a 500-cm^3 round-bottom flask equipped with a dropping funnel with a pressure-equalized tube and headed with a reflux condenser, the mixture of an appropriate (1*R*,4*R*)-2-arylidene-4-methyl-*p*-menthan-3-one **6** (0.049 mol), 7.8 g NaOH (0.196 mol), 60 cm^3 dimethylsulfoxide, 80 cm^3 water, 0.3 g SDS, and 10 cm^3 isopropyl alcohol was intensively refluxed, and the mixture of volatile products and water was collected in a dropping funnel. Water (bottom layer) was periodically returned to the reaction mixture. After distillation had finished (normally 7–8 h), the water-DMSO reaction mixture was substituted with a solution of 7.5 g potassium permanganate (0.048 mol) and 7.5 g sodium carbonate (0.070 mol) in 250 cm^3 water, and the collected organic layer was transferred from the dropping funnel to the flask. The resulting mixture was refluxed for 30 min, and then (1*R*,4*R*)-4-methylmenthan-3-one was steam distilled from the mixture, separated from water, and dried over Na_2SO_4. The obtained product is pure enough (purity 99.2 % according to GC–MS) to be further used without additional purification. An analytically pure sample (purity 99.8 % according to GC-MS) could be obtained by distillation (b.p.: 220–221 °C) as a colorless oil. TLC (hexane–ethyl acetate 25:1): $R_f = 0.35$; MS (EI): $m/z = 168, 153, 135, 126, 109, 97$; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 0.60$ (3H, d), 0.72 (3H, s), 0.83 (3H, d), 0.97 (3H, d), 1.15–1.35 (1H, m), 1.41–1.60 (2H, m), 1.61–1.86 (1H, m), 1.86–2.00 (1H, m), 2.00–2.15 (1H, m), 2.17–2.37 (2H, m) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 15.64, 17.57, 19.01, 22.01, 23.92, 29.45, 35.08, 36.90, 47.24, 51.19, 214.91$ ppm; $[\alpha]_D^{15} = +12.7°$ cm^2 g^{-1} ($c = 3.3$, $CHCl_3$); IR (neat): = 2950 (s), 2910 (s), 2855 (s), 1709 (s), 1455 (s), 1362 (s), 1278 (m), 1222 (m), 1120 (m), 1105 (m) cm^{-1}.

Acknowledgments Financial support from from the National Academy of Science of the Ukraine (project no. 0107U003550) is gratefully acknowledged.

References

1. Nielsen AT, Houlihan WJ (1968) The aldol condensation. In: Organic reactions, vol 16. Wiley Interscience, p 1
2. Mukaiyama T (1982) The directed aldol reaction. In: Organic reactions, vol 28. Wiley Interscience, p 203
3. Djerassi C, Burakevich J, Chamberlin JW, Elad D, Toda T, Stork G (1964) J Am Chem Soc 86:465
4. Eisenbraun EJ, Hanel PG, Schorno KC, Dilgen FS, Osiecki J (1967) J Org Chem 32:3010
5. dos Santos EM, Bogdan M, Victor MM, Tenius BSM, de Oliveira ER (2007) J Braz Chem Soc 18:370
6. Rupe H, Kambli E (1927) Justus Liebigs Ann Chem 459:195
7. Johnson WS (1937) J Am Chem Soc 65:1317
8. Akhrem AA, Titov YA (1970) Total steroid synthesis. Plenum Press, New York
9. Vashchenko VV (1997) Thesis, Cand Sci (Chem), Institute for Single Crystal, Kharkov
10. Kutulya LA, Vashchenko VV, Kuznetsov VP, Kulishov VI, Lakin EE (1995) Kristallografiya 40:1015
11. Vashchenko V, Dryshlyak T, Shkolnikova N, Kutulya L (1999) Mol Cryst Liq Cryst 328:245
12. Quesnel Y, Toupet L, Duhamel L, Duhamel P, Poirier J-M (1999) Tetrahedron Asymmetry 10:1015

13. Smith MB, March J (2007) March's advanced organic chemistry. Reactions, mechanisms and structure, 6th edn. Wiley, Hoboken, New Jersey
14. Evans DA (1984) Stereoselective alkylation reactions of chiral metal enolates. In: Asymmetric synthesis, vol 3. Academic Press, New York, p 1
15. Fieser LF, Fieser M (1959) Steroids. Reinhold Publishing Corp, New York
16. Tascioglu S (1996) Tetrahedron 52:11113
17. Ruasse M-F, Blagoeva IB, Ciri R, Garcia-Rio L, Leis JR, Marques A, Mejuto J, Monnier E (1997) Pure Appl Chem 69:1923
18. Buck KT, Boeing AJ, Dolfini JE, Glinka J (1987) Method of catalytically hydrolyzing α,β-unsaturated carbonyl compounds. EP 242934; (1988) Chem Abstr 108:114670x
19. Buck KT, Boeing AJ, Dolfini JE (1987) Method of producing benzaldehyde. US Patent 4673766; (1987) Chem Abstr 107: 156970e
20. Vashchenko V, Kutulya L, Krivoshey A (2007) Synthesis 2125
21. Hassner A, Mead TC (1961) Tetrahedron 20:2201
22. Vashchenko VV, Pivnenko NS, Kutulya LA, Petrenko AS, Iksanova SV, Goodby JW (2000) Russ Chem Bull 49:1218
23. Gottlieb HE, Kotlyar V, Nudelman A (1997) J Org Chem 62: 7512
24. Eisenbraun EJ, McElvain SM (1955) J Am Chem Soc 77:3383
25. Gurst JE (1992) J Chem Educ 69:774