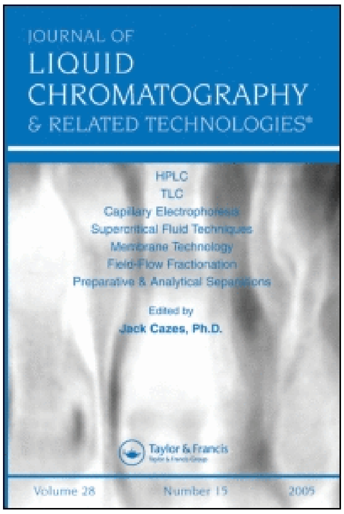

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

DEVELOPMENT OF CHROMATOGRAPHIC PROCEDURE FOR THE PURIFICATION OF 1,2-DIKETONE

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To cite this Article Deepika, P. , Sabharwal, K. N. , Sivaraman, N. , Srinivasan, T. G. and Vasudeva Rao, P. R.(2010) 'DEVELOPMENT OF CHROMATOGRAPHIC PROCEDURE FOR THE PURIFICATION OF 1,2-DIKETONE', Journal of Liquid Chromatography & Related Technologies, 33: 1, 97 — 108

To link to this Article: DOI: 10.1080/10826070903430415

URL: http://dx.doi.org/10.1080/10826070903430415

Journal of Liquid Chromatography & Related Technologies, 33:97–108, 2010

ISSN: 1082-6076 print/1520-572X online
DOI: 10.1080/10826070903430415

DEVELOPMENT OF CHROMATOGRAPHIC PROCEDURE FOR THE PURIFICATION OF 1,2-DIKETONE

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□ *α-diketones are important precursors for the synthesis of a wide variety of compounds. Many methods for the synthesis of 1,2-diketones using a variety of reagents have been reported. Almost all the methods result in the formation of by-products in small or major amounts. In this paper, the development of a column chromatographic method for the separation of a diketone from keto-ester is reported. The column conditions standardized for the purification of the diketone from keto-ester may also find application in similar cases involving the presence of more polar by-products formed along with the diketone during the course of the reaction.*

Keywords column chromatography, α-diketones, HPLC, octane-4,5-dione, potassium permanganate oxidation, TLC

INTRODUCTION

α-Diketones find wide utility in synthetic organic chemistry, particularly as intermediates in the preparation of more complex heterocyclic structures. Commercially, α-diketones are valuable intermediates for pharmaceutical products, dye-stuffs and perfumes. In the nuclear industry, classes of extractants known as the BTPs (Bis Triazinyl Pyridines) are candidates for the separation of the minor actinides from the high-level waste. These have been synthesized using α-diketones as precursors.[1–3] In recent years, BTBPs (Bis Triazinyl Bipyridines) and BATPs (Bis Annulated Triazinyl Pyridines), designed to mark an improvement over the BTPs have been also synthesized from the 1,2-diketones as precursors.[4,5]

A variety of methods for the synthesis of 1,2-diketones have been reported in the literature such as coupling of acid-chlorides using samarium diiodide,[6] coupling of acyl cyanides using ytterbium iodide[7] and the

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multistep selenium dioxide oxidation of various monoketones.[8] 1,2-Diketones are also available through oxidative procedures such as the "ene" reaction of singlet oxygen with alkenes in the presence of titanium alkoxide[9] or by the oxidation of acetylenes with $NaIO_4/RuO_2$.[10] Direct oxidation of olefins to 1,2-diketones by potassium permanganate in acetic anhydride is also an important route of synthesis.[11] Hindered 1,2-diaryl diketones have been prepared by the reaction of the corresponding aryl lithium with CO in THF[12] and the oxidation of acetylenes to α-diketones using palladium chloride in DMSO.[13] The practical application of many of these methods is limited by the use of expensive or less easily available reagents, harsh reaction conditions, number of steps involved in the work-up and difficult isolation of pure products.

In the present work on 2,6-bis (5,6-dipropyl-1,2,4-triazin-3-yl) pyridine (nPr-BTP), it was required to synthesize the α-diketone, octane-4,5-dione, as a precursor. Octane-4,5-dione was synthesized directly from trans-4-octene as per the synthesis procedure reported by Sharpless et al., using potassium permanganate in acetic anhydride medium.[11] This procedure results in the formation of the by-product, keto-acetate. We have developed and standardized the conditions for the column chromatographic separation of the synthesized octane-4,5-dione using permanganate/acetic anhydride procedure. The purified product was characterized using HPLC, FT-IR, GC-MS and NMR techniques.

EXPERIMENTAL

Reagents and Procedures

Octane-4,5-dione is a yellow coloured liquid with a characteristic odour. It was synthesized from trans-4-octene (+90%, Sigma Aldrich)[11] (Figure 1). All other chemicals used for the synthesis and subsequent work-up were of AR grade.

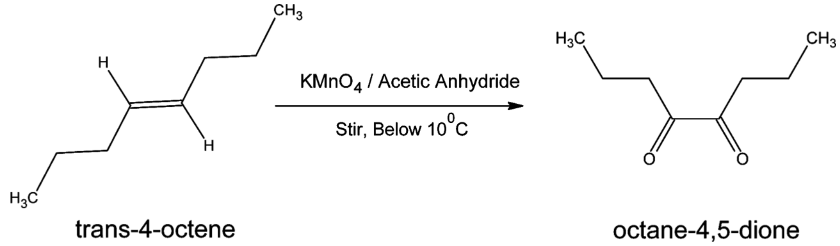

FIGURE 1 Synthesis of octane-4,5-dione.

Thin-Layer Chromatography was performed using TLC Aluminium Silica-gel 60 F_{254} Sheets (Merck) cut into small pieces of approx. 4 × 10 cm size. Fine capillaries were used to spot the compound, octane-4,5-dione. The TLC for the compound was performed in two different solvents, hexane, dichloromethane and 50:50 (v/v) hexane dichloromethane mixture respectively. The sheets were subsequently air-dried and placed in iodine chamber for spot visualization.

For column chromatography, a glass column of 2.5 cm dia was used. The height of the stationary phase loaded onto the column was maintained at approx. 40 cm for each experiment. The resultant bed-volume was calculated to be approx. 200 mL. Aluminium oxide (active, neutral Activity I-II Brockmann, Merck) was dried at 100°C for one hour prior to use. Alumina was loaded to the column by preparing slurry in hexane. The support was then conditioned by passing about two bed-volumes of the desired composition of the mobile phase to be used for elution. Similarly, silica-gel 60–120 Mesh (SISCO Research Lab, Mumbai), was also dried at 100°C for one hour before preparing a slurry of it in hexane and loading it onto the column. The column was then conditioned with the eluting solution as mentioned above. 2 mL ($\sim$1.8 g) of impure diketone was loaded to the alumina column for each run, while for the silica column, 4 mL ($\sim$3.6 g) of the impure compound was loaded. The eluate from the column was collected in fractions of 5–10 mL at a time in large number of tubes. These fractions were evaporated to dryness, re-dissolved in methanol (HPLC grade) and subjected to HPLC analysis. Fractions giving identical peak profiles were collected together and analyzed further for their complete characterization.

For HPLC studies, methanol (HPLC Grade) was used along with HPLC grade water (purified using Millipore) as the mobile phase.

Instrumentation

The HPLC system consisted of a solvent delivery pump (Jasco PU-1580), UV-VIS Spectrophotometric detector, reverse phase C18 column (Hypersil, 250 × 4.6 mm, 5 μm), and a 20 μl sample loop injector. The detection was carried out at 254 nm. The signal response from the detector was processed by Borwin Software.

The diketone was characterized using FT-IR (ABB FT-LA 2000 model), ^{1}H-NMR (JEOL GSX 400 MHz) and GC-MS (JEOL GC MATE-II) double focusing instrument with electron impact ionization as source. The FT-IR Spectrum was recorded using a KBr Pellet.

RESULTS AND DISCUSSION

Synthesis of Octane-4,5-dione

The synthesis of octane-4,5-dione by the oxidation of trans-4-octene using potassium permanganate in acetic anhydride resulted in an impure product. After work-up, the contaminants remaining were the keto-acetate and a small amount of the starting olefin as has also been reported earlier.[11] Distillation of this crude product with a rotary evaporator removed the un-reacted olefin, resulting in an impure product consisting of the desired compound, octane-4,5-dione along with the keto-acetate. A strong peak at 1232 cm^{-1} corresponding to C-O stretch in the FT-IR Spectrum of this impure octane-4,5-dione (Figure 2) was obtained after distillation, thereby confirming the presence of an ester impurity along with the product. Vacuum distillation of the impure diketone product has been investigated generally for further purification of the compound. However, owing to the high vapour pressure of octane-4,5-dione, we observed that losses were significantly higher for this compound through vacuum distillation and hence column chromatographic purification method was investigated in the present work.

Thin Layer Chromatography of Octane-4,5-dione

Prior to attempting the purification of the octane-4,5-dione in a chromatographic column, its behavior in thin layer chromatography was

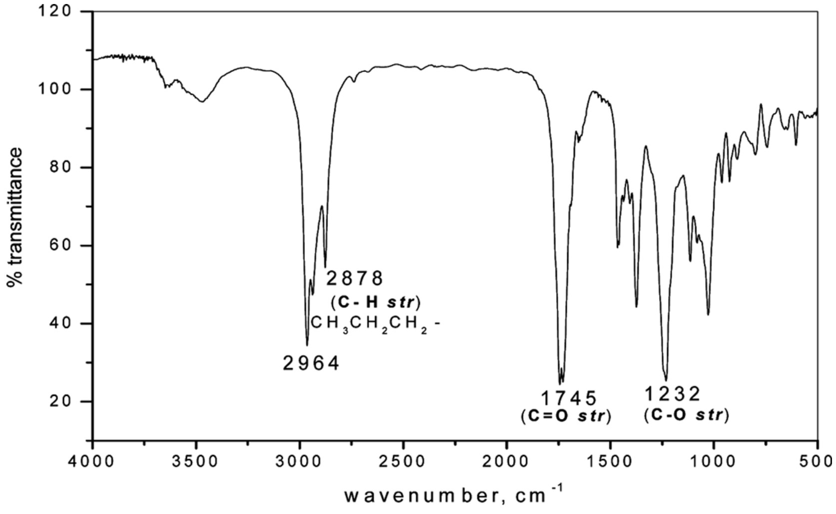

FIGURE 2 FT-IR Spectrum of impure product octane-4,5-dione.

analyzed. Two solvents were used for this purpose, hexane and dichloromethane. The TLC was performed in hexane, dichloromethane and 50:50 (v/v) hexane-dichloromethane mixture. It was observed that while the compound spot moved with the solvent front when dichloromethane was used as the mobile phase, there was no movement of the spot in hexane. In 50:50(v/v) hexane-dichloromethane medium, the spot resolved into two distinct spots with retention factors 0.5 and 0.8. Since α-diketone is less polar compared to the ester, it moved faster on the silica-gel stationary phase compared to the ester thereby resulting in a separation of the two in TLC. The TLC study was employed as the basis for the development of solvent for column chromatography.

HPLC Analysis of Octane-4,5-dione

HPLC analysis of octane-4,5-dione was performed during the course of its synthesis after work-up, and after rotary distillation at two wavelengths 220 and 254 nm. The results obtained are as shown in Figure 3. It is reported[11] that after the work up of the synthesized diketone, the only contaminants remaining are the keto-acetate and a small amount of the

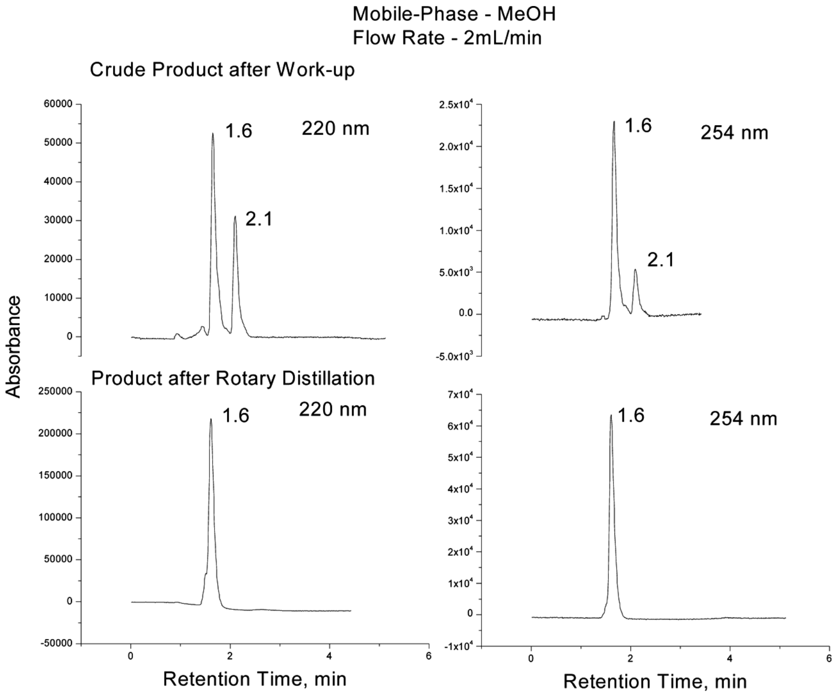

FIGURE 3 Octane-4,5-dione analyzed using HPLC after synthesis during work-up.

starting olefin. The HPLC of the crude product obtained after work-up in methanol as mobile phase at a flow-rate of 2 mL/min gave two peaks 1.6 and 2.1 minutes respectively at both the wavelengths. Distillation of the crude product on rotary evaporator removed the olefin and afforded the impure diketone along with the keto-acetate. This was also evident in the HPLC analysis by the removal of the peak at 2.1 minute (Figure 3). This peak thus corresponded to the olefin, which being more non-polar than the products formed in the reaction eluted later in an HPLC column. The single peak at 1.6 minute was subjected to isocratic elution in methanol-water mobile phase at the wavelengths 220 and 254 nm. At 220 nm, mainly a single peak was observed for different compositions of methanol-water mobile-phase. However at 254 nm, under isocratic elution conditions, it was observed that the single peak at 1.6 minute resolved into two peaks corresponding to α-diketone and keto-acetate as the polarity of the mobile phase was increased. The single peak at 220 nm is attributable

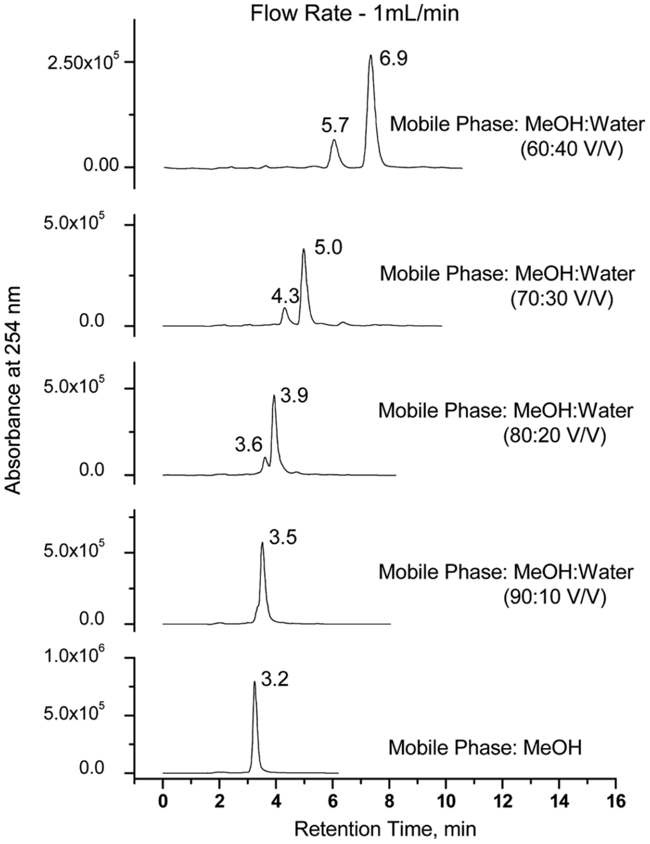

FIGURE 4 Isocratic Elution of impure octane-4,5-dione at 254 nm during HPLC analysis.

to the diketone; though the keto-ester absorbs at 254 nm, its lower molar extinction co-efficient at 220 nm relative to that of the diketone makes its detection at this wavelength difficult. Consequently, a wavelength of 254 nm was used for characterizing the compound, octane-4,5-dione, with the HPLC technique. For better resolution, the flow rate for the isocratic elution of the diketone at 254 nm was maintained at 1 mL/min (Figure 4). It was observed that a single peak with retention time 3.25 min was obtained when the mobile phase was methanol and a flow rate of 1 mL/min was employed, and this peak resolved into two peaks with retention times 3.6 and 3.9 minutes respectively, when 80:20 (v/v) methanol-water was used as the mobile phase. The resolution of the peaks increased for 70–30 and 60–40 (v/v) compositions of methanol-water mobile phase. In an HPLC column, α-diketone will elute later compared to the ester. This can be explained again in terms of the polarities of the two compounds. Diketone being more non-polar than the ester will be retained on the reverse phase column whereas ester will be more soluble in the polar mobile-phase and hence will elute faster. From Figure 5, it is seen that the retention times for pure octane-4,5-dione increases with decrease in the methanol content in the mobile-phase or increase in polarity of the mobile phase. While the diketone elutes at 3.2 minute for methanol mobile-phase, it elutes at 3.9 minute for 80–20 (v/v) methanol-water composition of the mobile phase, it appears at 6.9 minutes for 60–40 (v/v) methanol-water mobile-phase. In fact, the retention times show an exponential decrease as the polarity of the mobile phase is

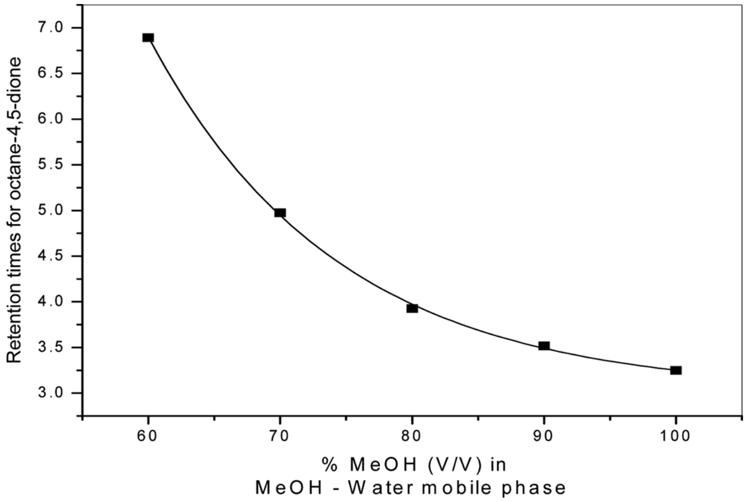

FIGURE 5 Variation of retention time for pure octane-4,5-dione with changing polarity of the mobile phase in HPLC. (Detection – 254 nm, Flow Rate – 1 mL/min).

decreased. Therefore, when the polarity of the mobile phase is reduced, diketone tends to elute faster being more soluble in the less polar mobile-phase whereas when polarity of the mobile phase is increased, the diketone tends to spend more time in the HPLC column. From this isocratic elution pattern, it was decided to study the purity of octane-4,5-dione as obtained after the column chromatography using 65–35 (v/v) methanol-water mobile phase and at a flow rate of 1 mL/min. Hence, the different fractions collected from the column were subjected to HPLC analysis using 65–35 (v/v) methanol-water mobile phase at a flow rate of 1 mL/min in the HPLC column.

Column Purification of Octane-4,5-dione

Neutral Alumina Column

Based on the thin layer chromatography as well as HPLC results, column purification for the impure octane-4,5-dione was attempted using a neutral alumina column. The mobile phase first employed for the purpose was 25% (v/v) dichloromethane in hexane. The flow-rate was maintained at 2 mL/min during the column run. The eluate was collected in fractions of 5 mL at a time. Different fractions were collected and analyzed using HPLC, but none of the fractions were obtained as pure. Hence, an attempt was again made to purify the diketone by reducing the polarity of the mobile-phase i.e., by using hexane as the mobile-phase using neutral alumina column. However no movement of the band was observed. Hence the polarity of the mobile phase was increased to 10% (v/v) dichloromethane in hexane, but again the band movement was found to be very slow for practical purposes. Further increase in polarity resulted in fractions, which when analyzed by HPLC were found to be impure. Therefore, the neutral alumina column was found to be not very effective for achieving separation of the diketone from the ester under the above experimental conditions.

Silica-gel Column

Due to the unsatisfactory results obtained using a neutral alumina column, it was decided to use a silica-gel column for the purification of diketone i.e., octane-4,5-dione. In this case, the mobile phase employed was 15% (v/v) dichloromethane in hexane. Owing to its lower polarity, diketone was expected to elute first and it was indeed observed to be the case. It took approximately two hours for the first yellow coloured band of the compound to elute since the time impure diketone was loaded onto the column. The flow rate was maintained at 5 mL/min during the column run. The eluted fractions were collected in fractions of 10 mL at a time.

About 100 fractions were collected using 15% (v/v) dichloromethane in hexane as the mobile-phase till the entire yellow band got eluted. All the fractions collected were subjected to HPLC analysis with methanol–water, 65:35 (v/v) as mobile-phase at a flow rate of 1 mL/min.

From the HPLC results obtained, it was seen that the fractions eluted with 15% (v/v) dichloromethane in hexane were essentially pure and gave a single peak throughout with a retention time of 5.7 minute (Figure 6). All these fractions were collected together as one fraction and subjected to FT-IR, NMR and GC-MS analysis.

The polarity of the column was slowly raised to 25% dichloromethane in hexane, then 50% dichloromethane in hexane and finally pure dichloromethane was passed through the column for complete elution. Fractions obtained with these higher polarities of the mobile-phase were impure and

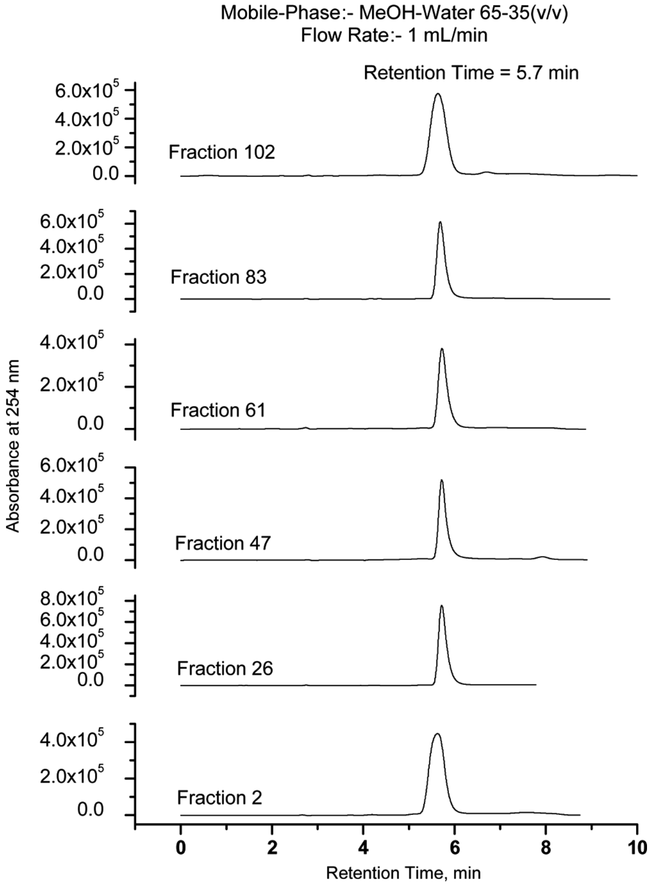

FIGURE 6 Pure octane-4,5-dione fractions obtained from Silica-gel column with mobile phase 15% (v/v) dichloromethane in hexane as analyzed by HPLC.

gave 2–3 peaks in the HPLC analysis. At this point it was observed that while the diketone peak intensity had decreased, peaks corresponding to other impurities present in smaller quantities were becoming prominent. Fractions eluted with pure dichloromethane were also impure and gave multiple peaks in the HPLC chromatogram. Hence, it was found difficult to elute the ester in pure form and characterize it as was done for the diketone.

The percentage yield of diketone after synthesis followed by column work was 43%. This was recovered in five times the bed-volume. This yield was better compared to the yields obtained by vacuum distillation and hence the loss of octane-4,5-dione in the chromatographic purification procedure was minimal.

Therefore, a silica-gel column with mobile-phase 15% (v/v) dichloromethane in hexane was found to be the best for the separation of the α-diketone, octane-4,5-dione, from the more polar reaction by-product, keto acetate.

Characterization of Octane-4,5-dione

From the FT-IR Spectrum of pure octane-4,5-dione (Figure 7), it can be seen that the sharp peak at 1712 cm^{-1} corresponds to C=O (*str*) while the peaks at 2966–2878 cm^{-1} correspond to the C—H (*str*) of the alkyl groups. The absence of the peak at 1232 cm^{-1} corresponding to C—O (*str*) clearly indicates the absence of any ester impurity.

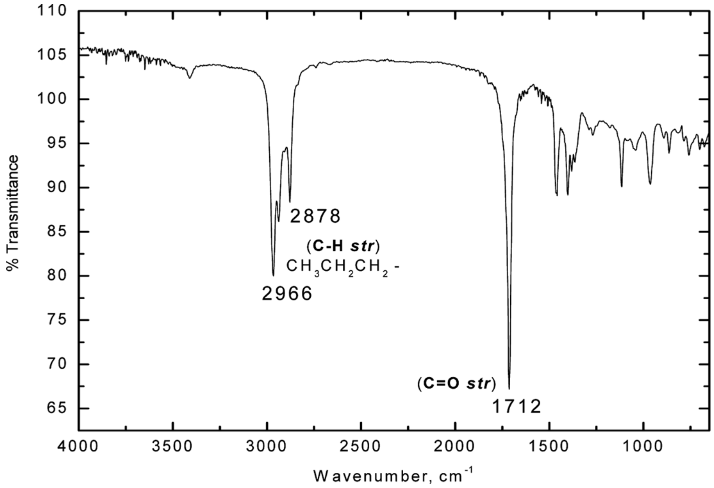

FIGURE 7 FT-IR Spectrum of pure product octane-4,5-dione.

The result from GC-MS for the pure octane-4,5-dione is as follows: 1.75 min, 100%, m/z 71 calculated for $CH_3CH_2CH_2CO$; 2.25 min, 42.7%, m/z 142 calculated for $CH_3CH_2CH_2COCOCH_2CH_2CH_3$.

The result from ^{1}H-NMR ($CDCl_3$) for the pure octane-4,5-dione is as follows:

δ 2.665–2.647 (t, 4H, $J = 0.02$ Hz, two $-CH_2-CO-$); δ 1.497–1.588 (m, 4H, $J = 0.02$ Hz, two $-CH_2-$); δ 0.850–0.888 (t, 6H, $J = 0.02$ Hz, two CH_3-).

The above results clearly indicate that the synthesized compound is octane-4,5-dione. The characteristic spectra confirm the purity of the compound as obtained by the column chromatography method.

CONCLUSIONS

A column chromatographic procedure was developed and standardized for the purification of α-diketones from keto-esters. It was found that almost all of the synthesized diketone could be recovered in high purity from a silica-gel column using 15% (v/v) dichloromethane in hexane as mobile phase. Silica column was found to be more suitable for the purification of octane-4,5-dione over neutral alumina. For the same dimensions of both the stationary phases, higher loading capacity of the compound over silica stationary phase could be achieved. Faster flow-rate could be achieved over silica stationary phase without affecting the band-separations and the band-movement was also relatively faster. Most importantly, a very clean and convenient separation of the product from the impurity could be achieved using a silica stationary phase.

It is also proposed that the given column conditions standardized for the purification of the diketone from keto-ester may also find application in similar other cases involving the presence of a more polar by-product formed along with the diketone during the course of the reaction.

ACKNOWLEDGMENT

The authors are grateful to Sophisticated Analytical Instrument Facility (SAIF), IIT Madras for ^{1}H-NMR and GC-MS Spectra.

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