

SYNTHESIS OPTIMIZATION OF THE BAEYER-VILLIGER OXIDATION OF 3-METHYLCYCLOHEXANONE

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Abstract:

Several attempts were made to synthesize 3-methyl- ϵ -caprolactone (I) free of its 5-methyl- ϵ -caprolactone (II) isomer based on the Baeyer-Villiger reaction of 3-methylcyclohexanone, using the inorganic oxidant oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) in its organic and aqueous phase. The best result was achieved with the aqueous phase at low temperature and a long reaction time. Although the reactions failed to produce very satisfactory yields, this alternative method proved quite promising for the synthesis objective.

Keywords:

Baeyer-Villiger. Lactones. Optimization.

OTIMIZAÇÃO SINTÉTICA DA REAÇÃO DE BAEYER-VILLIGER DE 3-METILCICLOEXANONA

Resumo:

Várias tentativas para a obtenção sintética de 3-metil- ϵ -caprolactona (I) livre de seu isômero 5-metil- ϵ -caprolactona (II), a partir da reação de Baeyer-Villiger de 3-metilcicloexanona, foram realizadas com o oxidante inorgânico “oxone” ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$), em fase orgânica e aquosa. O melhor resultado encontrado foi em fase aquosa, baixa temperatura e tempo de reação prolongado. Apesar dos rendimentos das reações não terem sido muito satisfatórios, este método alternativo se mostrou bastante promissor para o fim sintético pretendido.

Palavras chave:

Baeyer-Villiger. Lactonas. Otimização.

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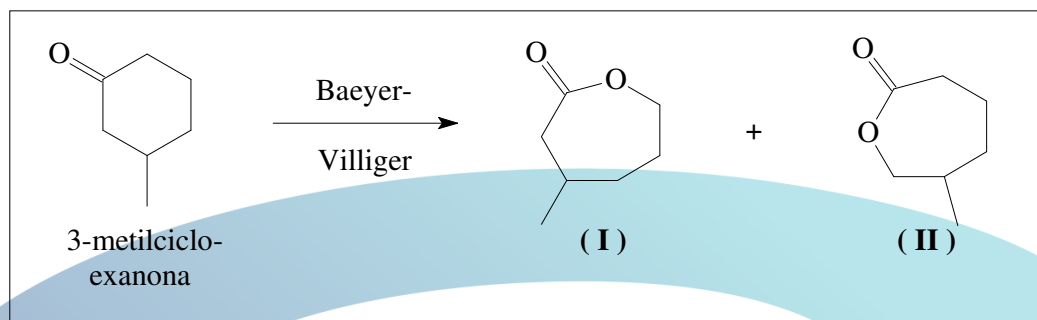
Introduction

The Baeyer-Villiger oxidation reaction is a classical process of organic transformation which converts ketones into esters by treating them with peroxyacids or hydrogen peroxide (BAEYER & VILLIGER, 1899; BAEYER & VILLIGER, 1900; CAREY & GIULIANO, 2016). These reactions are characterized by high stereospecificity and regioselectivity (CRUDDEN et al., 2000) as in the esterification of equatorial camphor-derived bicyclic ketones (TURNER, 1950), in which the retention of configuration occurs. The peroxyacids most commonly used in this type of reaction are peracetic, meta-chloroperbenzoic, monoperoxymaleic and trifluoroperacetic acid (BURTON et al., 1997). The latter is usually the most widely employed acid because of its higher oxidation rate. However, it may cause transesterification between the starting ester product and trifluoroperacetic acid (HAWTHORNE et al., 1958; EMMONS & LUCAS, 1955). The mechanism of reaction using peroxyacids, which is well described in the literature (HOUSE, 1972; SOLOMONS & FRYHLE, 2011; SMITH, 2013), involves in the initial step a nucleophilic addition of the hydroperoxy to the ketone carbonyl and subsequent rearrangement of the cyclic intermediate state to an ester through the migration of the corresponding alkyl group.

Cyclic ketones can also undergo Baeyer-Villiger oxidation, in this case generating cyclic esters (have functional group - (C = O) -O-) known as lactones (IUPAC, 2014), many of them found in nature and important for taste of many fruits (BERGER, 2007). The most common and most stable lactones are those with five- or six-membered rings, as they exhibit lower strain of bond angles than four- and seven-membered lactones. However, stable bicyclic and macrocyclic lactones are still found (MAHAJAN & RESCK, 1997; SOLOMONS & FRYHLE, 2011). The seven-membered ring lactones studied in this paper present reasonable stability at pH near neutral. They are called ϵ -lactones or ϵ -caprolactones because they are derived from caproic acid. Derivatives of ϵ -caprolactones are used as polymers and materials for use in surgery (KÖPNICK et al., 2002) and some polymers that play important roles in drug delivery (SISSON et al., 2013).

Cyclic symmetrical ketones generate only a lactonic product. On the other hand, asymmetrical ketones generate products according to the different degrees of migration facility of the alkyl group bound to the ketone carbonyl, with a predominance in the migration of tertiary alkyl groups, followed by secondary and lastly primary alkyl groups (HOUSE, 1972; VOLLHARDT & SCHORE, 2014). Several lactones originating from this type of reaction are described in the literature (SAUERS, 1959; MURRAY et al., 1956).

With respect to 3-methylcyclohexanone, with non-substituted alpha to carbonyl positions, the Baeyer-Villiger reaction necessarily yields the isomeric mixture of the lactones 3-methyl- ϵ -caprolactone (I) and 5-methyl- ϵ -caprolactone (II):



Overberger & Kaye (1967) carried out the asymmetric synthesis of lactone (I) in two ways: the first via high-dilution dehydration of 6-hydroxy-3-methylhexanoic acid, and the second via a Baeyer-Villiger reaction of 3-methylcyclohexanone using trifluoroacetic acid as oxidant and CH_2Cl_2 as solvent. The Baeyer-Villiger reaction of 3-methylcyclohexanone was also explored by Hirano et al. (1991) in a non-asymmetric synthesis, using oxone as the oxidant, Al_2O_3 as the supporting reagent and CH_2Cl_2 as the solvent. In both cases, the two isomeric lactones (I) and (II) were formed with low yields, but attempts at separation by column chromatography or gas chromatography were unsuccessful (OVERBERGER & KAYE, 1967). Three other variants of the Baeyer-Villiger reaction of 3-methylcyclohexanone are reported in the literature, involving liquid phase catalytic oxidation (SEROV et al., 1980) and oxidation with hydrogen peroxide/urea (KIRSCHKE & OBERENDER, 1972; KIRSCHKE & OBERENDER, 1973), which also yield the isomeric mixture (I) and (II) in nonselective proportions.

This paper reports on the optimization of 3-methyl- ϵ -caprolactone (I) production for purposes of synthesis (BATALINI & BIEBER, 2001), starting from 3-methylcyclohexanone, through several attempted reactions, using the inorganic oxidant oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) in organic phase with support reagent and in aqueous phase.

Methods

⇒ Baeyer-Villiger reaction of 3-methylcyclohexanone with humidified Al₂O₃ acid [15] (Table 1 – reaction 1):

Forty-five mmol (53 g) of oxone (2KHSO₅.KHSO₄.K₂SO₄), followed by 18 mmol (2.2 mL, 2.01 g) of 3-methylcyclohexanone, were added at room temperature to a suspension of 20 g of humidified Al₂O₃ acid (stirred vigorously with 3 mL of distilled water in a closed vessel) in 150 mL of CH₂Cl₂. The reaction was maintained under these conditions for 24 h. The remaining solid was filtered and washed with 50 mL of CH₂Cl₂. Rotary evaporation of the solvent then yielded a light yellow oily liquid which was identified by ¹H NMR as the mixture of lactones (I) and (II) (MURRAY et al., 1956) obtained in the proportion of 52:48%, respectively (Table 1 – reaction 1).

⇒ Baeyer-Villiger reaction of 3-methylcyclohexanone with humidified SiO₂ (Table 1 – reaction 2):

Twenty-seven mmol (16.6 g) of oxone (2KHSO₅.KHSO₄.K₂SO₄), followed by 18 mmol (2.2 mL; 2.01g) of 3-methylcyclohexanone, were added at room temperature, to a suspension of 20 g of humidified SiO₂ (stirred vigorously with 3 mL of distilled water in a closed vessel) in 80 mL of CH₂Cl₂. The reaction was maintained under these conditions for 24 h. The organic phase was then washed with 20 mL of NaHCO₃ and dried with Na₂SO₄. The solvent was then subjected to rotary evaporation, yielding an oily yellow residue that was stored at -7°C. A ¹H NMR analysis indicated a percentage of lactones (I) and (II) of 60:40%, respectively (Table 1 – reaction 2).

⇒ Baeyer-Villiger reaction of 3-methylcyclohexanone in aqueous phase (Table 1 – reactions 3 to 6):

Reactions 3 to 6 in Table 1 were performed using the same procedure, but varying the temperature and reaction time.

A suspension of 75 mmol (46.1 g) of oxone in 120 mL of distilled water, at 0°C and with constant stirring, was added to a solution of 122.6 mmol (15 mL; 13.7 g) of 3-methylcyclohexanone in 120 mL of distilled water. The reaction was kept in the time and

temperature conditions described in Table 1. The organic phase was extracted with three aliquots of 20 mL of CH₂Cl₂ and the combined organic extracts were washed with 20 mL of NaHCO₃ and 20 mL of NaHSO₃. The organic phase was dried with Na₂SO₄. After rotary evaporation of the solvent, the colorless oily liquid was subjected to rapid distillation using a heat gun, resulting in a colorless oil that was stored at -7°C and identified by ¹H NMR as the mixture of lactones (I) and (II) in the proportions described in Table 1; boiling point = 79-80°C (1.0 mmHg).

¹H NMR (CCl₄) – data corresponding to reaction 6 – Table 1):

3-methyl-ε-caprolactone (I): 1.07 (d, 3H, J≅7.5Hz); 1.43-2.07 (m, 5H); 2.43-2.60 (m, 2H); 4.17 (t, 2H, J≅5.2Hz).

5-methyl-ε-caprolactone (II): 0.90 (d, 2H, overlapping at 1.07 (d, 3H) of (I)); 1.43-2.07 (m, 5H); 2.43-2.60 (m, 2H); 4.00-4.10 (m, 2H).

Results and discussion

Table 1 describes the different oxidation reactions of 3-methylcyclohexanone in organic and aqueous phases.

Table 1 – Baeyer-Villiger oxidation reactions of 3-methylcyclohexanone using the inorganic reagent oxone

Reaction no.	Temperature (°C)/ Time (h)	Solvent/Support reagent	(%) Lactones (I) and (II)		Yield (%)
1	30 / 24.0	CH ₂ Cl ₂ / Al ₂ O ₃	52	48	----- *
2	30 / 24.0	CH ₂ Cl ₂ / SiO ₂	60	40	23.3
3	30 / 1.0	H ₂ O / ----	75	25	27.5
4	30 / 2.0	H ₂ O / ----	84	16	7.8
5	0 / 2.0	H ₂ O / ----	59	41	38.9
6	-7 / 20.0	H ₂ O / ----	92	08	6.0

* Incomplete transformation.

In general, reactions 1 and 2 with oxone in organic medium (CH₂Cl₂) produced satisfactory yields, except for Reaction 1, whose yield could not be calculated due to

incomplete transformation to the product, although the proportion of lactones (I) and (II) remained in the equilibrium ratio.

In the aqueous phase and at room temperature (reactions 3 and 4 – Table 1), the percentage of lactone (I) increased considerably compared to that of lactone (II) with increasing reaction time, but the yield of the reaction decreased markedly. Reaction 5, carried out in aqueous medium at low temperature, showed a better yield in a shorter reaction time, but without the predominance of lactone (I). In aqueous oxidizing medium, the most promising result of 3-methyl- ϵ -caprolactone (I) predominance was achieved at a temperature below zero (reaction 6 – Table 1), by prolonging the reaction time. Despite the low yield obtained in this reaction, the proportion of lactone (I) can be considered to be of sufficient purity for purposes of synthesis.

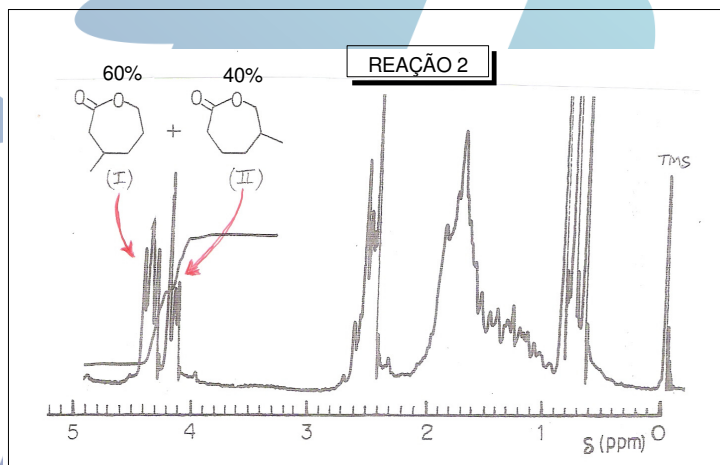


Figure 1 – ^1H NMR spectrum of the isomeric mixture of (I) and (II) obtained in reaction 2 (organic phase)

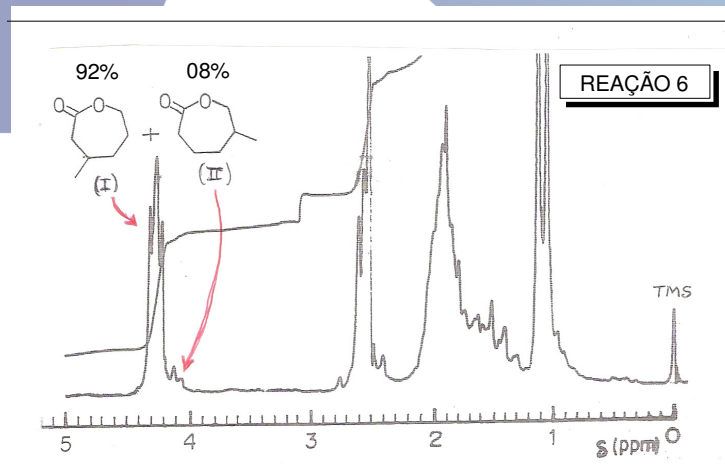


Figure 2 – ^1H NMR spectrum of the isomeric mixture of (I) and (II) obtained in reaction 6 (aqueous phase)

Conclusions

The reactions tested in this study characterize alternative methods of Baeyer-Villiger oxidation of asymmetric cyclic ketone 3-methylcyclohexanone, aiming to achieve the predominance of one of the isomers, 3-methyl- ϵ -caprolactone (I), for subsequent purposes of synthesis. The most promising result was obtained with the reaction in aqueous medium, which contributes toward a cleaner environment.

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