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Thallium Trinitrate Mediated Ring Contraction of Monocyclic Ketones: Stereochemical Aspects

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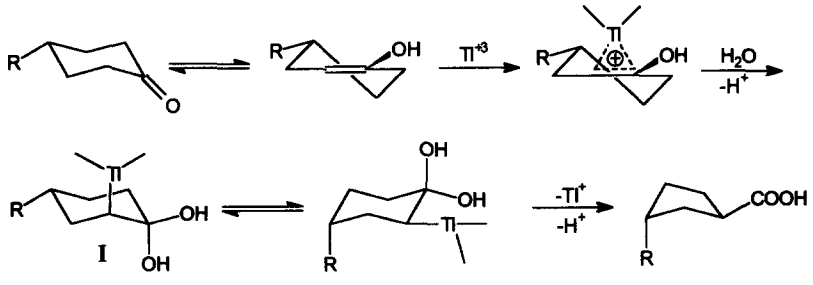
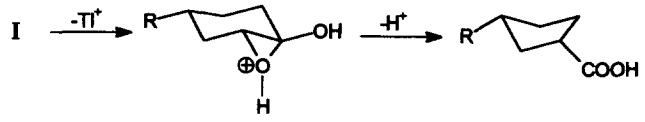
Abstract: The reaction of 3- and 4-alkylcyclohexanones with thallium trinitrate (TTN) leads to the alkylcyclopentanecarboxylic acids in good yields and with high degree of stereoselectivity. The ring contraction of 2-methylcyclohexanone gives poor yields and 2,6-dimethylcyclohexanone does not undergo contraction. The observed diastereoselectivities of the reactions agree with the mechanism proposed by McKillop et al. © 1997 Elsevier Science Ltd. All rights reserved.

The ring contraction of cyclohexanone and of some alkylcyclohexanones promoted by thallium (III) salts has already been described by Wiberg and Koch[1] and by McKillop et al.,[2] but the stereochemical aspects of this reaction have not been studied yet. Furthermore, two different mechanisms for the contraction reaction were proposed.[1,2] According to Wiberg's mechanism (Scheme 1), the ring contraction of 4-alkylcyclohexanone, for example, should lead to *trans*-3-alkylcyclopentanecarboxylic acid, whereas according to McKillop's proposal (Scheme 2), the *cis*-isomer is expected.



Scheme 1



Scheme 2

The thallium (III) salt mediated contractions of other cyclic ketones, such as cyclobutanone,[3] (1S,5S)-bicyclo-[3.2.1]-2-octanone,[4] steroid ketones[5] and α-tetralone[6] are also described in the literature.

In connection with our studies toward the synthesis of natural products containing the cyclopentane unit, and due to our long standing interest in thallium (III) salt,[7] we decided to investigate the stereochemical aspects of the ring contraction, starting with simple monocyclic ketones (Table 1). The reactions were performed with thallium trinitrate trihydrate, at room temperature, using methylene dichloride as solvent.[8]

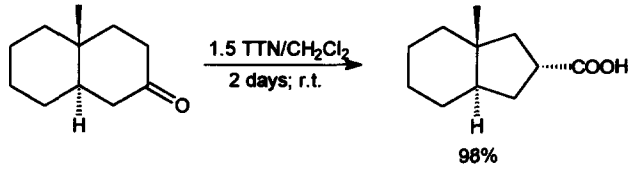
The ring contraction of 4-methylcyclohexanone (entry 1, Table 1) furnished a 4:1 mixture of two diastereoisomers, while 4-*t*-butylcyclohexanone (entry 2) showed total diastereoselectivity.

For the 3-alkylcyclohexanones, the regiochemical aspect becomes relevant, since two enol forms can be postulated ($\Delta^{1,2}$ and $\Delta^{1,6}$). In these cases (entries 3 and 4), the observed regioselectivity was the same as in the alkylation reactions[9] and in the ring contraction mediated by SeO_2,[10] where the $\Delta^{1,6}$-enol form predominates.[11] Moreover, this selectivity was higher for 3-*t*-butylcyclohexanone[12] than for 3-methylcyclohexanone.

In contrast to 3- and 4-alkylcyclohexanones, the presence of a methyl group at the α-carbonyl position of the cyclohexanones hinders the ring contraction reaction. Thus, 2-methylcyclohexanone (entry 5) gave only 36% of the *cis*-2-methylcyclopentanecarboxylic acid (originated from the kinetic enol). We were unable to detect the presence of the 1-methylcyclopentanecarboxylic acid, which would come from the thermodynamic enol form.[13] Finally, the 2,6-dimethylcyclohexanone (entry 6) did not undergo contraction, the only isolated product being the 2,6-dimethyl-2-cyclohexen-1-one, together with 33% of the starting material, even after 9 days under reaction.

The configuration of the carboxylic acids was determined by ^{13}C-NMR.[14]

The extension of this reaction to more complex cyclic ketones is under way in our laboratory. In a preliminary experiment, the *trans*-fused 10-methyl-3-decalone gave the acid in 98% yield (Scheme 3).



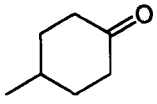
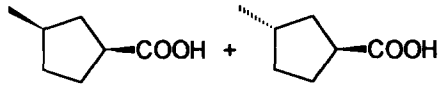
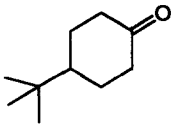
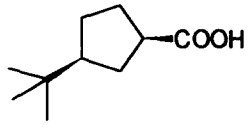
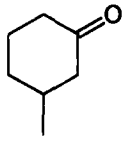
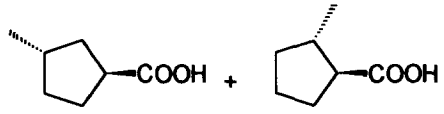
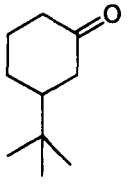
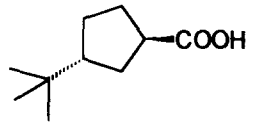
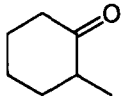
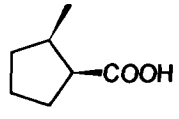
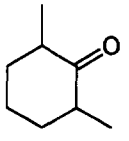
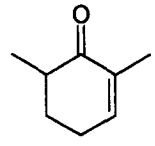
98%

Scheme 3

Experimental

General procedure: To a solution of the ketone (5mmol) in CH_2Cl_2 (20mL), was added TTN (Table 1). The mixture was stirred at room temperature, for the time indicated in Table 1, and then filtered through Celite®. The filtrate was washed with brine, dried over magnesium sulfate, and the solvent was evaporated.

Table 1. Reaction of Monocyclic Ketones with TTN.3H$_2$O in CH_2Cl_2 at Room Temperature.

Entry	Substrate	Conditions	Product (ratio[a])	Yield
1		1.1 eq. TTN 1 day	 (4 : 1)	97%
2		1.1 eq. TTN 1 day		87%
3		1.5 eq. TTN 2 days	 (2 : 1)	98%
4		1.5 eq. TTN 2 days		65%
5		2 eq. TTN 3 days		36%[b,c]
6		3.5 eq. TTN 9 days		52%[d]

[a]determined by ^{1}H-NMR; [b]determined by gas chromatography;
[c]plus other unidentified products; [d]plus 33% of 2,6-dimethylcyclohexanone.

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REFERENCES AND NOTES

1. Wiberg, K. B.; Koch, W. *Tetrahedron Lett.* **1966**, 1779-1782.
2. McKillop, A.; Hunt, J.D.; Taylor, E.C. *J. Org. Chem.* **1972**, *37*, 3381-3382.

3. Salaun, J.; Garnier, B.; Conia, J.M. *Tetrahedron* **1974**, *30*, 1423-1426.
4. Irwin, A.J.; Jones, J.B. *J. Org. Chem.* **1977**, *42*, 2176-2177.
5. a) Mincione, E.; Barraco, P.; Forcellese, M.L. *Gazz. Chim. Ital.* **1980**, *110*, 515-517. b) Maione, A.M.; Romeo, A.; Cerrini, S.; Fedeli, W.; Mazza, F. *Tetrahedron* **1981**, *37*, 1407-1413.
6. Taylor, E.C.; Chiang, C.S.; McKillop, A.; White, J.F. *J. Am. Chem. Soc.* **1976**, *98*, 6750-6751.
7. a) Ferraz, H.M.C.; Ribeiro, C.M.R.; Grazini, M.V.A.; Brocksom, T.J.; Brocksom, U. *Tetrahedron Lett.* **1994**, *35*, 1497-1500. b) Ferraz, H.M.C.; Ribeiro, C.M.R. *Synth. Commun.* **1992**, *22*, 399-404. c) Ferraz, H.M.C.; Brocksom, T.J.; Pinto, A.C.; Abla, M.A.; Zocher, D.T.H. *Tetrahedron Lett.* **1986**, *27*, 811-814.
8. This was the best solvent for mediating the ring contraction. Other conditions, tested with cyclohexanone, were TTN/MeOH,[4] TTN/CH_2Cl_2/TMOF[15] and TTA/CH_2Cl_2, but no good results were obtained. TTN/CH_3CN was tested with 4-*t*-butylcyclohexanone, giving *cis*-3-*t*-butylcyclopentanecarboxylic acid in good yield.
9. Mundy, B.F. *J. Chem. Ed.* **1972**, *49*, 91-96.
10. Granger, R.; Boussinesq, J.; Girard, J.P.; Rossi, J.C.; Vidal, J.P. *Bull. Soc. Chim. Fr.* **1969**, 2806-2812.
11. We have repeated this reaction under Wiberg's conditions (35% aq. solution of $HClO_4$, TTN, r.t.), obtaining 3-methylcyclopentanecarboxylic acid as the main product (80% by ^{1}H-NMR, 1:10/ *cis:trans*), together with a minor amount (20%) of *trans*-2-methylcyclopentanecarboxylic acid (total yield: 93%). We believe that this apparent discrepancy between our own results and that described by Wiberg[1] (2-methylcyclopentanecarboxylic acid as the main product) may be attributed to the lack of ^{13}C-NMR analysis in the 1960s. It must also be emphasized that the relative configuration of the product was not assigned in the Wiberg's work.
12. Prepared by the reaction of 2-cyclohexenone with *t*-Bu(Me)Cu(CN)Li_2.[16]
13. When this reaction was performed under Wiberg's conditions, we observed a preponderant formation of the elimination product (2-methyl-2-cyclohexen-1-one), which is in agreement with the original work[1]. This result also suggests that our conditions (CH_2Cl_2 as solvent) are useful when ring contraction is the desired reaction for this type of substrate.
14. ^{13}C NMR (50MHz, $CDCl_3$): *cis*-2-methylcyclopentanecarboxylic acid[17,18] (C1 48.4; C2 37.4; C3 33.7; C4 23.7; C5 27.3; C=O 182.0; CH_3 16.1); *trans*-2-methylcyclopentanecarboxylic acid[17] (C1 51.8; C2 39.5; C3 34.9; C4 24.6; C5 30.0; C=O 183.1; CH_3 19.6); *cis*-3-methylcyclopentanecarboxylic acid[18] (C1 43.8; C2 38.7; C3 35.2; C4 34.0; C5 29.0; C=O 183.0; CH_3 19.8); *trans*-3-methylcyclopentanecarboxylic acid (C1 42.8; C2 37.7; C3 34.0; C4 34.6; C5 29.6; C=O 183.5; CH_3 20.0); *cis*-3-*t*-butylcyclopentanecarboxylic acid (C1 43.7; C2 31.9; C3 51.4; C4 26.4; C5 29.0; C=O 183.0; C(q) 32.3; CH_3 27.6); *trans*-3-*t*-butylcyclopentanecarboxylic acid (C1 43.4; C2 (or C5) 30.2; C3 50.1; C4 27.9; C5 (or C2) 30.5; C=O 183.1; C(q) 32.0; CH_3 27.5).
15. a) Taylor, E.C.; Robey, R.L.; Liu, K.T.; Favre, B.; Bozimo, H.T.; Conley, R.A.; Chiang, C.S.; McKillop, A.; Ford, M.E. *J. Am. Chem. Soc.* **1976**, *98*, 3037-3038. b) Taylor, E.C.; Conley, R.A.; Johnson, D.K.; McKillop, A. *J. Org. Chem.* **1977**, *42*, 4167-4169.
16. Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *J. Org. Chem.* **1984**, *49*, 3938-3942.
17. Canonne, P.; Plamondon, J. *Can. J. Chem.* **1989**, *67*, 555-564.
18. Hoberg, H.; Ballesteros, A.; Sigan, A.; Jegat, C.; Milchereit, A. *Synthesis* **1991**, 395-398.

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