Tetrahedron xxx (2013) 1–4

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solvent-induced, selective rearrangement of hydrogen cubane-1,4-dicarboxylate to hydrogen cuneane-2,6-dicarboxylate

Gábor Durkó *, István Jalsovszky

Department of Organic Chemistry, Institute of Chemistry, Eötvös Loránd University, P.O. Box 32, H-1518 Budapest, Hungary

ARTICLE INFO

Article history:
Received 8 February 2013
Received in revised form 26 March 2013
Accepted 15 April 2013
Available online xxx

Keywords:
Strained molecules
Rearrangement
Chemoselectivity

ABSTRACT

The rearrangement of cubane-1,4-dicarboxylic acid in water to cuneane-2,6-dicarboxylic acid is presented. The reaction is not a transition metal catalyzed, rather a solvent-promoted transformation, and the reaction proceeds via the semi-dissociated form of the cubane diacid, hydrogen cubane-1,4-dicarboxylate. No other, 1,3-disubstituted cuneane isomer is formed. The reaction is significantly accelerated by the addition of 1 equiv of base, suggesting that the hydrogen cubane-1,4-dicarboxylate ion plays a key role in this new type of rearrangement.

1. Introduction

Transition metal catalyzed skeletal rearrangements of strained systems have been known since the 1970s.[1–5] Among these, one of the first described examples is the transformation of cubane to cuneane. Silver(I) perchlorate or palladium(II) chloride catalyzed this rearrangement which, in the case of substituted cubanes, afforded mixtures of cuneane isomers (Fig. 1).[6–8] According to the proposed mechanism, oxidative addition of the metal ion to a C–C bond is followed by carbonium ion formation and rearrangement.[9]

Lithium(I) with a weakly coordinating carborane anion was also used to induce a skeletal rearrangement on cubane and some analogous compounds, however, these rearrangements presumably follow a mechanism different from the transition metal catalyzed transformation.[10] Apart from Ag(I), Pd(II), and Li(I), no other species was found to induce a rearrangement to cuneane. Theoretical calculations suggest that protonation[11] or single electron transfer oxidation[12] of cubane may also result in a rearrangement leading either to cuneane or to pentalenes, but experimental proof seems to be controversial.[13]

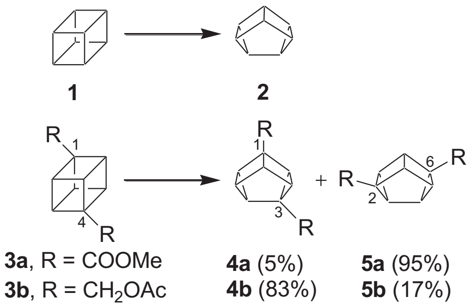

Fig. 1. Cubane–cuneane rearrangement.

Ring opening reactions affording tricyclooctadiene or cyclooctatetraene, have also been reported. Conversion of cubane to *syn*-tricyclooctadiene is induced by rhodium(I) ions[14] or lithium diisopropylamide.[15] This intermediate can be converted to cyclooctatetraene upon heating.[16] Direct thermal ring opening of cubanes is also possible without catalyst[17] and even without solvent.[18] It was also reported that thermal rearrangement of cuneane affords the isomeric cyclooctatetraene via semibullvalene.[19] 4-Iodo-1-vinylcubane was found to rearrange to 4-vinyl-*trans*-β-iodostyrene through a cyclooctatetraene intermediate.[20]

2. Results and discussion

Previous studies on the cubane–cuneane rearrangement were limited to the parent compound and a few ester derivatives, while substituent effects seem to have a significant influence on the outcome of the reaction.[6] Also no detailed study has been devoted to the conditions of the rearrangement. Our aim was to investigate how solvent polarity, temperature, and the concentration of the catalyst or other additives affect reaction rate and product/isomer distribution. Whereas previous studies have been dealt with less

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* Corresponding author. Tel.: +36 1 372 2500/1216; fax: +36 1 372 2592; e-mail address: gdurko@elte.hu (G. Durkó).

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http://dx.doi.org/10.1016/j.tet.2013.04.056

Please cite this article in press as: Durkó, G.; Jalsovszky, I., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.04.056

polar derivatives, we have chosen a water-soluble model compound, cubane-1,4-dicarboxylic acid (**6**).

2.1. The effect of catalyst concentration

Upon investigation of the silver(I) catalyzed rearrangement of cubane-1,4-dicarboxylic acid (**6**) in water using silver nitrate as catalyst, we have found that the catalytic effect of the Ag(I) ion could be initiated using 10^{-4} equiv of the catalyst (Fig. 2).

Rearrangement also occurs in lower concentrations, independent from Ag(I) concentration. We got the same yields (2–4% at 135 °C/1.6 bar/3 h) even without any added silver nitrate. Although deionized, conductivity grade water and purified materials were used, obviously the silver(I) concentration could not be reduced to 'zero'—ICP-MS analysis of the starting materials and the solvent showed that the 'residual' silver(I) concentration was 4.6 ng/mL, which is 5×10^{-7} equivalents relative to the cubane diacid. However, this amount is well below the 10^{-4} equivalent limit, therefore no catalytic effect can be attributed to silver(I) ions in such low concentrations.

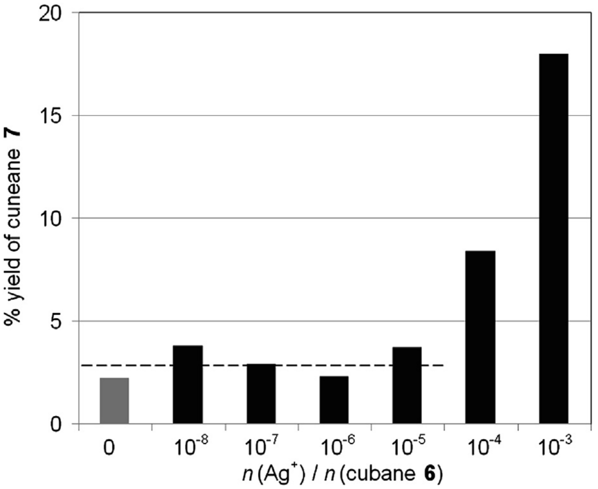

Fig. 2. The effect of silver(I) concentration on the rearrangement of cubane **6** to cuneane **7** (10 mg of **6** in 0.5 mL aqueous $AgNO_3$ solution at 135 °C/3 h) (Yields were determined by ^1H NMR after workup.).

2.2. The effect of solvent

The 'silver-free' rearrangement of cubane-1,4-dicarboxylic acid (**6**) to cuneane-2,6-dicarboxylic acid (**7**) was examined in various solvents at (or near to) reflux temperature (Table 1). Transformation to cuneane was observed only in polar protic media (water and carboxylic acids). In polar aprotic solvents decomposition (e.g., in DMF and diglyme) or cage opening to cyclooctatetraene-1,4-dicarboxylic acid (**8**) occurred (e.g., in DMSO and also in sulfolane). This thermal ring opening affording cyclooctatetraene was also observed in polar protic solvents at elevated temperature (Fig. 3).

2.3. The effect of pH and acid dissociation

In order to get a better insight into the role of protic media in the rearrangement, the pH dependence of the reaction was examined in water at 135 °C/1.6 bar, and was found to be significant. Strongly acidic media (pH 2, HCl/H_2O) inhibited cuneane formation, so a direct acid-catalyzed mechanism is unlike. This assumption is in agreement with the work of Olah and his co-workers who protonated cubane-1,4-dicarboxylic acid (**6**) in superacids, and the resulting cubyl carboxonium ions did not rearrange.[22]

Table 1
Rearrangement of cubane-1,4-dicarboxylic acid (**6**) in various media

Solvent	Bp [°C]	Conditions	Yield of **7** [%]	Yield of **8** [%]
Water	100	Reflux/11 h	3%	—
Acetic acid	119	Reflux/12 h	5%	—
		185 °C/5 bar/12 h	—	25%
Propanoic acid	141	Reflux/12 h	5%	3%
Pentanoic acid	186	Reflux/12 h	—	21%
Toluene	111	Reflux/12 h	—	—
1-Nitropropane	131	Reflux/12 h	—	—
DMF	153	Reflux/12 h	—[a]	—
Diglyme	162	Reflux/12 h	—[a]	—
DMSO	189	180 °C/12 h	—	36%
Sulfolane	285	180–190 °C/12 h	—	71%
H_2SO_4 98%	—	25 °C/12 h	—	—
HBr 62%	—	100 °C/12 h	—[b]	—
HCl 37%	—	Reflux/12 h	—[c]	—

[a] Starting material partially decomposed.
[b] Bond cleavage and HBr addition[21] was observed.
[c] Starting material fully decomposed.

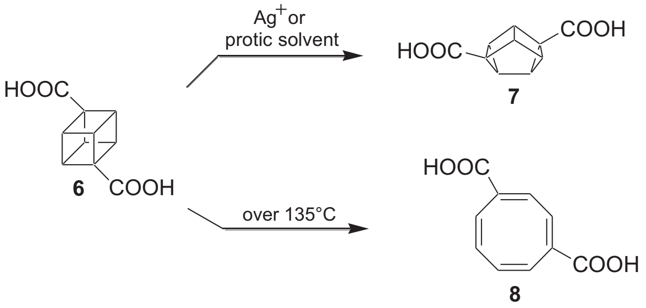

Fig. 3. Rearrangement of cubane-1,4-dicarboxylic acid (**6**).

However, the addition of base (potassium hydroxide) resulted in higher yields. The maximum cuneane yield was achieved with 1 molar equivalent of KOH relative to the dicarboxylic acid **6** (Fig. 4), which corresponds to the semi-dissociated form, hydrogen cubane-1,4-dicarboxylate (**6b**). The same results were obtained with other bases, such as sodium hydroxide, potassium carbonate and sodium carbonate. After neutralization and workup of the samples, NMR

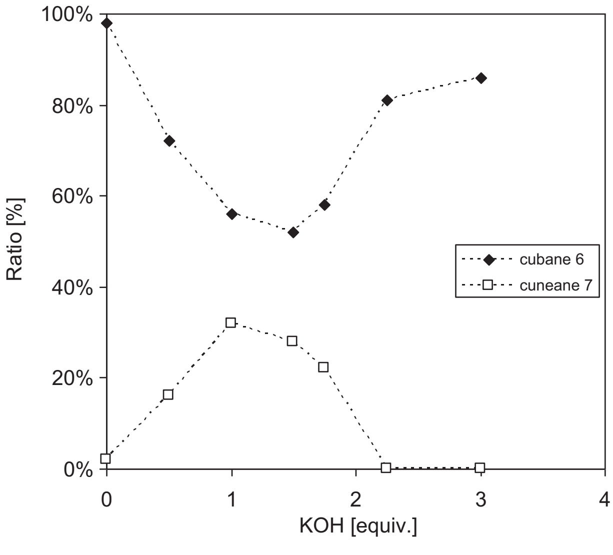

Fig. 4. The effect of acid dissociation on the rearrangement of cubane **6** to cuneane **7** (10 mg of **6** in 0.5 mL aqueous KOH solution at 135 °C/3 h) (The ratio of **6** and **7** in the crude product was determined by ^1H NMR after workup, using the solvent signal as an internal integration reference.).

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analysis showed only the presence of the cuneane product and the unreacted starting material, along with an insoluble tarry byproduct. The material balance (composition of the crude reaction mixture) is presented on Fig. 4.

The dependence of species distribution on the base/acid ratio in these solutions was calculated with Hyss2009 software[23] (Fig. 5). The higher the concentration of the semi-dissociated form of the cubane diacid (**6b**), the higher the ratio of its rearrangement to cuneane. No cuneane was formed when more than 2 equiv of base were added, in this case the diacid is fully dissociated and virtually no hydrogen cubane-1,4-dicarboxylate (**6b**) is present.

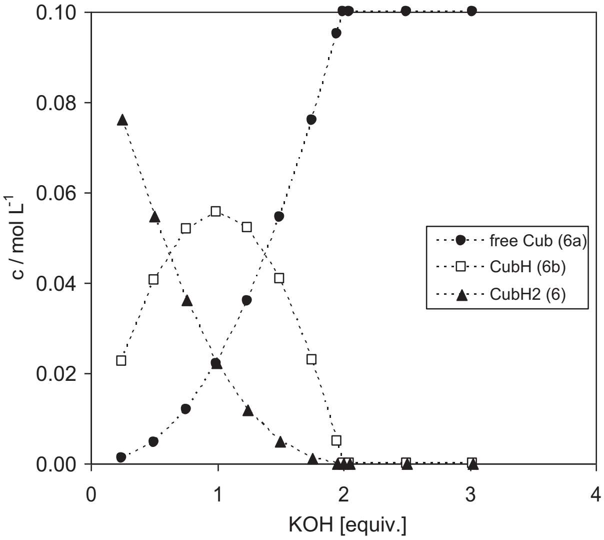

Fig. 5. Calculated species distribution in solutions of cubane diacid **6** containing different quantities of KOH (Cub: cubane-1,4-dicarboxylate (**6a**), CubH: hydrogen cubane-1,4-dicarboxylate (**6b**), CubH$_2$: cubane-1,4-dicarboxylic acid (**6**)).

The concentration dependence of the silver-free rearrangement reaction also supports the key role of the semi-dissociated form. Cuneane yield is in inverse proportion to the initial cubane concentration: the more dilute the solution, the higher the yield. As cubane-1,4-dicarboxylic acid (**6**) is a weak acid (pK_a values are 5.43 and 6.23, respectively[24]), in dilute solutions the ratio of the dissociated form (**6b**) is higher. When the carboxyl function was transformed to dimethyl amide to prevent dissociation, no cuneane was formed.

2.4. The effect of temperature

Preliminary experiments in aqueous media were carried out at reflux conditions, but later we changed to sealed disposable glass ampoules, which have the advantage that the solution can be heated to over 100 °C under pressure, and it is also easier to keep away interfering silver(I) ions as if flasks and reflux condensers were used. Elevating the temperature over 100 °C enabled higher cuneane yields but that is limited by the decomposition of cuneane-2,6-dicarboxylic acid (**7**) and the thermal ring opening of the starting cubane dicarboxylic acid **6** to cyclooctatetraene diacid **8**, which is favored at higher temperatures (Fig. 6).

2.5. Isomer selectivity

Under the conditions applied in our experiments (solvent: H$_2$O, 135 °C/1.6 bar, 1 equiv KOH added) the 2,6-derivative (**7**) was formed selectively, whereas previous reports describe the formation of mixtures of cuneane isomers in the rearrangement of dimethyl cubane-1,4-dicarboxylate (**3a**), induced by silver(I) perchlorate in benzene or toluene.[6–8] We also observed this selectivity in the case of the silver(I) nitrate catalyzed rearrangement of the cubane diacid **6** in water. While the diacid and its dimethyl ester can not be directly compared, a likely explanation to this difference might be that there is an equilibrium between the 1,3- and 2,6-disubstituted cuneane isomers, and the higher temperature applied in our experiments favors the formation of the 2,6-derivative, which is thermodynamically more stable.[7]

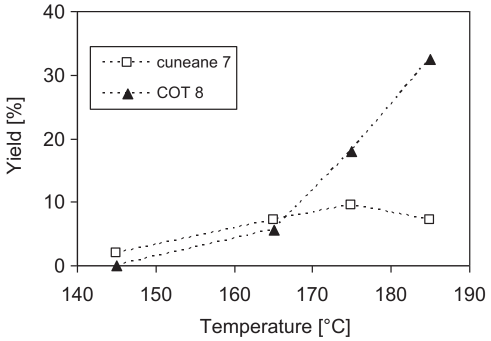

Fig. 6. Product distribution as a function of temperature in the rearrangement of cubane **6** to cuneane **7** and cyclooctatetraene (COT) **8** in pressurized water (10 mg **6** in 0.5 mL H$_2$O, reaction time: 60 min).

The decrease in the concentration of the cuneane product along with the increase of cyclooctatetraene concentration upon prolonged heating (Fig. 6) may suggest that the cuneane diacid also rearranges to the corresponding cyclooctatetraene derivative.[19] However, when we heated in pure form, cuneane-2,6-dicarboxylic acid (**7**) did not rearrange to cyclooctatetraene diacid **8** neither in protic nor in aprotic media nor under solvent-free conditions, only slow decomposition was observed, affording an insoluble tarry material.

2.6. Mechanism

A possible mechanism for the reaction is shown on Fig. 7. In the second step there is a 1,2 bond shift from C(4)–C(5) to C(4)–C(2). It should be noted that, because of the symmetry of intermediate **9**, C(3) and C(5) are equivalent, so a C(4)–C(3) to C(4)–C(2) bond shift is equally possible, and because of the chirality of cuneane-2,6-dicarboxylic acid (**7**), the alternative route leads to an enantiomeric product. In this step the positive charge is transferred from a four-membered ring to a five-membered ring, which might be one of the driving forces of the rearrangement.

3. Conclusion

As predicted by quantum chemical calculations[11,12] and shown by an earlier example,[10] species other than transition metal ions may be able to bring about skeletal rearrangements in strained ring systems. However, no attempt was made to carry out the rearrangement of cubane derivatives in polar media. In this paper we presented that cubane-1,4-dicarboxylic acid (**6**) rearranges selectively to the corresponding 2,6-cuneane derivative **7** in aqueous media with no transition metal ion added. While obviously the presence of a trace amount of silver(I) ions can not be fully excluded, the following observations prove indirectly that this reaction is not silver catalyzed, rather a solvent-promoted transformation, and the reaction proceeds via the semi-dissociated form of the cubane diacid, hydrogen cubane-1,4-dicarboxylate (**6b**):

- The dilution effect—the more dilute the solution of cubane diacid, the higher the conversion rate to cuneane.

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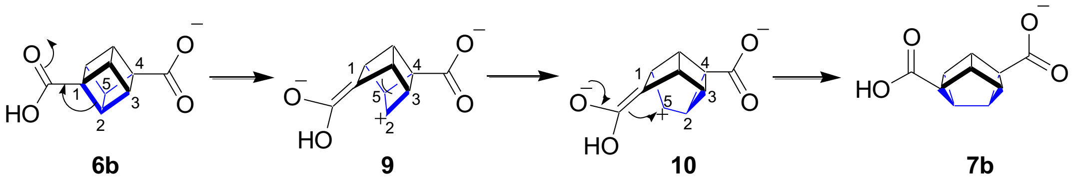

Fig. 7. Proposed mechanism for the rearrangement of hydrogen cubane-1,4-dicarboxylate (**6b**).

- The base effect—the reaction was significantly accelerated by the addition of a base, and the maximum yield was achieved at 1 equiv of base relative to the cubane diacid, which corresponds to the maximum concentration of hydrogen cubane dicarboxylate (**6b**). The addition of more than 1 equiv of base diminished reaction rate, and more than 2 equiv (complete dissociation) prevented rearrangement.
- The acid effect—rearrangement was also prevented by the addition of a strong acid, which protonates the dissociated forms of the cubane dicarboxylic acid.
- The silver ion effect—addition of silver(I) ions to the samples in concentrations even 2 orders of magnitude higher than originally present, did not affect the rate of rearrangement.

4. Experimental section

All conversions were determined by ^{1}H NMR in DMSO-d_6 after workup, using the solvent peak as an internal integration reference. Chemical shifts (δ) are given in parts per million relative to tetramethylsilane. NMR spectra were recorded on a BRUKER Avance 250 spectrometer (^{1}H: 250.13 MHz, ^{13}C: 62.9 MHz). Starting materials were checked for trace amounts of metals (such as Ag, Pd and Li) by ICP-MS.

4.1. Cubane-1,4-dicarboxylic acid (6)

Dimethyl cubane-1,4-dicarboxylate (**3a**) was prepared according to a known literature method.[25] The diester was converted to the diacid upon treatment with NaOH/H_2O, then precipitated with HCl/H_2O, and washed thoroughly with distd water. The diacid was recrystallized twice from glacial acetic acid, and was dried in vacuo prior to use. Compound **6** is a white powder. δ_H (250 MHz, DMSO-d_6): 4.10 (s, 6H). δ_C (62.5 MHz, DMSO-d_6): 172.7 (2C, carbonyl), 55.8 (2C, quaternary), 46.3 (6C, CH).

4.2. General procedure for the rearrangement of diacid 6

10 mg (0.052 mmol) of diacid **6** and 500 μL of 0.104 M potassium hydroxide solution (0.052 mmol), made from deionized (conductivity grade) water, were sealed in a 2 mL glass ampoule under argon, and heated to 135 °C for 3 h. After acidification with a slight excess of dilute hydrochloric acid, the solvent was evaporated, and the sample was dissolved in DMSO-d_6 for NMR analysis.

4.3. Cuneane-2,6-dicarboxylic acid (7)

Compound **7** was prepared for reference using a method described in the literature,[7,8] and was found to be identical with the product of the solvent-induced rearrangement of cubane diacid **6**. Pale brown powder. δ_H (250 MHz, DMSO-d_6): 3.05–2.98 (m, 4H), 2.94 (m, 2H). δ_C (62.5 MHz, DMSO-d_6): 176.8 (2C, carbonyl), 48.8, 48.1, 45.3, 43.1. IR (ATR): 1662, 1440, 939, 858, 736 cm^{-1}. HRMS: m/z calculated for $C_{10}H_8O_4$–H^+ (M–H^+): 191.0350; found: 191.0354.

Acknowledgements

We thank Dr. András Bartha (Geological Institute of Hungary) and Dr. Mihály Óvári (Eötvös Loránd University, Budapest, Hungary) for ICP-MS analysis, and Dr. Szabolcs Béni (Semmelweis University, Budapest, Hungary) for an HRMS measurement. The European Union and the European Social Fund have provided financial support to the project under the grant agreement No. TÁMOP 4.2.1./B-09/KMR-2010-0003.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.056. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Paquette, L. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 2584–2586.
2. Dauben, W. G.; Buzzolini, M. G.; Schallhorn, C. H.; Whalen, D. L.; Palmer, K. J. *Tetrahedron Lett.* **1970**, *11*, 787–790.
3. Paquette, L. A. *Synthesis* **1975**, *11*, 347–357.
4. Bishop, K. C., III. *Chem. Rev.* **1976**, *76*, 461–486.
5. Griffin, G. W.; Marchand, A. P. *Chem. Rev.* **1989**, *89*, 997–1010.
6. Cassar, L.; Eaton, P. E.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 6366–6368.
7. Roux, M. V.; Dávalos, J. Z.; Jiménez, P.; Notario, R.; Castano, O.; Chickos, J. S.; Hanshaw, W.; Zhao, H.; Rath, N.; Liebman, J. F.; Farivar, B. S.; Bashir-Hashemi, A. *J. Org. Chem.* **2005**, *70*, 5461–5470.
8. Bényei, G.; Jalsovszky, I.; Vajda, A.; Jákli, A.; Demus, D.; Rao, S.; Prasad, K.; Fodor-Csorba, K. *Liq. Cryst.* **2006**, *33*, 689–696.
9. Byrd, J. E.; Cassar, L.; Eaton, P. E.; Halpern, J. *J. Chem. Soc., Chem. Commun.* **1971**, 40–41.
10. Moss, S.; King, B. T.; Meijere, A. de; Kozhushkov, S. I.; Eaton, P. E.; Michl, J. *Org. Lett.* **2001**, *3*, 2375–2377.
11. Abboud, J.-L. M.; Koppel, I. A.; Dávalos, J. Z.; Burk, P.; Koppel, I.; Quintanilla, E. *Angew. Chem., Int. Ed.* **2003**, *42*, 1044–1046.
12. Schreiner, P. R.; Wittkopp, A.; Gunchenko, P. A.; Yaroshinsky, A. I.; Peleshanko, S. A.; Fokin, A. A. *Chem.—Eur. J.* **2001**, *7*, 2739–2744.
13. Fokin, A. A.; Tkachenko, B. A.; Gunchenko, P. A.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 146–149.
14. Cassar, L.; Eaton, P. E.; Halpern, J. *J. Am. Chem. Soc.* **1970**, *92*, 3515–3518.
15. Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1975**, *31*, 1419–1426.
16. Eaton, P. E.; Galoppini, E.; Gilardi, R. *J. Am. Chem. Soc.* **1994**, *116*, 7588–7596.
17. Martin, H.-D.; Pföhler, P.; Urbanek, T.; Walsh, R. *Chem. Ber.* **1983**, *116*, 1415–1421.
18. Prokudin, V. G.; Lagodzinskaya, G. V.; Dubikhin, V. V.; Nazin, G. M.; Romanova, L. B.; Eremenko, L. T. *Kinet. Catal.* **2005**, *46*, 800–804.
19. Hassenrück, M.; Martin, H.-D.; Walsh, R. *Chem. Ber.* **1988**, *121*, 369–372.
20. Carroll, V. M.; Harpp, D. N.; Priefer, R. *Tetrahedron Lett.* **2008**, *49*, 2677–2680.
21. Eaton, P. E.; Millikan, R.; Engel, P. *J. Org. Chem.* **1990**, *55*, 2823–2826.
22. Head, N. J.; Rasul, G.; Mitra, A.; Bashir-Heshemi, A.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 12107–12113.
23. Alderighi, L.; Gans, P.; Ienco, A.; Peters, D.; Sabatini, A.; Vacca, A. *Coord. Chem. Rev.* **1999**, *184*, 311–318.
24. Cole, T. W.; Mayers, C. J.; Stock, L. M. *J. Am. Chem. Soc.* **1974**, *96*, 4555–4557.
25. Bliese, M.; Tsnaktsidis, J. *Aust. J. Chem.* **1997**, *50*, 189–192.

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