ORGANIC LETTERS

2011
Vol. 13, No. 8
2142–2144

Selective Hydroxylation of Methane by Dioxiranes under Mild Conditions

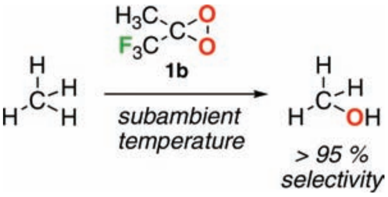
Cosimo Annese,[†] Lucia D'Accolti,[†] Caterina Fusco,[†] and Ruggero Curci*[,†,‡]

*Dipartimento Chimica, CNR-ICCOM, Università di Bari "A. Moro", v. Amendola 173,
70126 Bari, Italy, and Department of Chemistry, Brown University, Providence,
Rhode Island 02912, United States*

curci@ba.iccom.cnr.it

Received February 21, 2011

ABSTRACT



The direct conversion of methane to methanol at low temperatures was achieved selectively using dioxiranes 1a,b either in the isolated form or generated *in situ* from aqueous potassium caroate and the parent ketone at a pH close to neutrality. Results suggest that the more powerful dioxirane TFDO (1b) should be the oxidant of choice.

The direct oxyfunctionalization of methane under mild conditions continues to pose a major challenge to the chemical community. A highly efficient and *selective* oxidation of methane to methanol is difficult, primarily because of the ease of overoxidation to HCH═O and to CO_2.[1]

The catalytic cycle using methane monooxygenase enzymes (MMO) to achieve the oxidation of methane has attracted the interest of scientists engaged in the development of biological methods for the production of commercial chemicals and for the degradation of toxic materials.[1,2]

On the other hand, the development of metal–catalyst systems for the *direct* oxidation of methane to methanol has been one of the major goals in catalysis.[3] Considerable progress has been made in understanding the chemical requirements for transition metal "activation" of carbon–hydrogen bonds.[4] However, in most cases the catalysts typically suffered from irreversible reduction and bulk metal formation, with consequent poor selectivity.[3,4]

Recently, using a solid triazine-based covalent platinum complex catalyst, the efficient conversion of methane to methanol in concentrated H_2SO_4 at ca. 200 °C, via CH_3O-SO_3H, was reported.[5] The major drawback of this novel method is the use of fuming sulfuric acid, which poses significant limitations regarding materials and costs.

The remarkable chemical reactivity of dimethyldioxirane[6] (DMDO) **1a** and of methyl(trifluoromethyl)dioxirane[7] (TFDO) **1b** (Figure 1) has been previously demonstrated.

Figure 1. Common dioxiranes in isolated form.

Using dioxiranes, hydrocarbons can be selectively oxygenated in what appears to be a highly stereoselective concerted process.[8] In the hydroxylation of "unactivated"

[†] Università di Bari "A. Moro".

[‡] Brown University.

(1) For example, see: Murray, L. J.; Lippard, S. J. *Acc. Chem. Res.* **2007**, *40*, 466. See also references cited therein.

(2) Crabtree, H. *Chem. Rev.* **1995**, *95*, 987.

(3) (a) De Vos, D. E.; Sels, B. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 30. (b) Jones, C. J.; Taube, D.; Periana, R. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4626. (c) Shilov, A. E.; Shullpin, G. B. *Chem. Rev.* **1997**, *97*, 2879.

(4) (a) Wolf, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 3351. (b) Baerns, M.; Ross, J. R. H. In *Perspectives in Catalysis*; Thomas, J. A., Zamaraev, K. I., Eds.; Blackwell: Oxford, 1992.

(5) Palkovits, R.; Antonietti, M.; Khun, P.; Thomas, A.; Schüth, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6909.

(6) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.

(7) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749.

(8) For a recent review of dioxiranes and C–H bond oxy-functionalization, see: Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1.

10.1021/ol2004676

C−H bonds, high tertiary vs secondary selectivities (R_s^t from 15 to > 250) can be routinely achieved.[7−9]

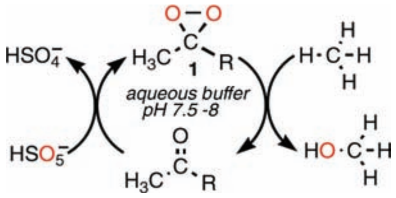
We recently reported on the direct dioxirane oxyfunctionalization of structurally complex alkanes, such as 2,4-didehydroadamantane, binor-S, and cubane.[8,9]

The many facets of selective oxyfunctionalization of alkanes using dioxiranes have been reviewed.[8]

One of the remaining challenges in dioxirane chemistry is the direct functionalization of methane to methanol. Despite its high technological interest, this important aspect of dioxirane reactivity has not yet been reported. Herein we report on the application of dioxiranes to the direct, remarkably low-temperature oxidation of methane to methanol with high reactivity and selectivity. Results presented herein provide a significant breakthrough for this key transformation.

We have employed dioxiranes **1a** and **1b** either in the isolated form or generated *in situ*. Solutions of isolated dioxiranes **1a** and **1b** in acetone or 1,1,1-trifluoropropanone (TFP), which were 0.06−0.1 M and 0.6−1.0 M respectively, were obtained adopting procedures already described in detail.[6,7]

Scheme 1. Methane Oxidation with Dioxiranes Generated *in Situ*



Alternatively, dioxiranes *in situ* were generated in buffered aqueous solutions (pH 7.5−8) using potassium peroxomonosulfate[10]($KHSO_5$)/ketone mixtures according to an established protocol (Scheme 1).[11]

Initially, oxidations were carried out in a pressure vessel charged with a cold dioxirane solution and pressurized at 2.5 atm with methane gas (Table 1, entry 1). At a temperature of 0 °C, the vessel pressure gradually decreased with time, signaling the progressive uptake of methane gas. In parallel, a significant decrease in dioxirane concentration was monitored (cf. note *f*, Table 1). After a 24 h reaction time, the mixture was analyzed by NMR and the amount of methanol product determined by calibrated GC. Starting with 99.5% enriched [^{13}C]methane, ^{13}C NMR spectroscopic analysis of the final reaction mixtures confirmed that methanol is the largely predominant liquid-phase product generated (Figure 2).

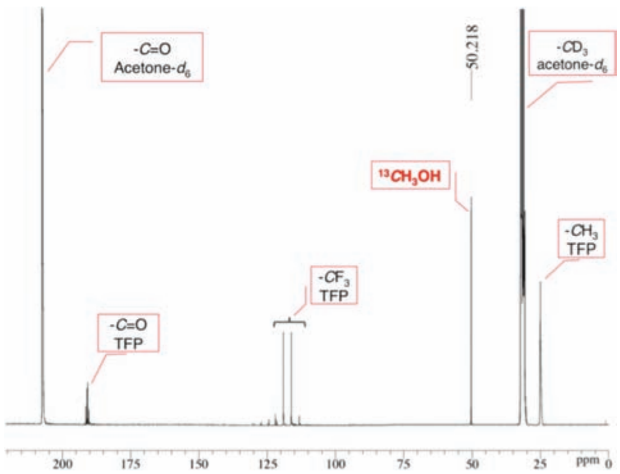


Figure 2. {^{1}H}^{13}C NMR (100 MHz, acetone-d_6) spectrum of the reaction mixture resulting from oxidation of 99.5% enriched [^{13}C]methane with isolated TFDO (**1b**) at 2.5 atm, temp 0 °C, solvent acetone/TFP 4:1 (0.5 mL of reaction mixture brought to 1 mL volume with acetone-d_6 solvent).

Based on the above findings, we were able to establish that the transformation is also feasible at atmospheric pressure. Accordingly, a dioxirane solution was placed in a sealed glass flask and a known amount of CH_4 gas slowly bubbled through the solution via a side tube.

The solution was stirred and kept at subambient temperature (from −10 to 3 °C). After an appropriate reaction time, the amount of methanol formed and of residual dioxirane were determined (Table 1, entries 2−4).

The data show that, using the powerful TFDO in acetone, the CH_3OH yield is > 95%, with 15% conversion after a 24 h reaction time (entry 2). The methanol yield was also > 95% employing water as the main solvent, although at a lower conversion (ca. 7%) (entry 3). As expected, with the less effective DMDO oxidant in water, a longer reaction time (72 h) is required to form CH_3OH with similar methane conversion (ca. 5%) (entry 4). Noteworthy, in none of the cases above were overoxidation products detected. Therefore, the selectivity observed is over 95% under the given conditions.

In addition, we found that methane oxidations can also be carried out in buffered aqueous media by employing dioxiranes generated *in situ* (Table 1, entries 5 and 6).

In this procedure, the apparatus and conditions were quite similar to those above, except the reaction flask was initially charged with a mixture of the parent ketone (i.e., TFP or acetone) and excess $KHSO_5$ aqueous solution, buffered at pH 7.5. We found that, with a 24 h reaction time at 2−5 °C, methane oxidation also affords methanol as the only product detectable (Table 1, entries 5 and 6).

Control experiments showed that reactions carried out omitting the ketone precursor of dioxirane failed to oxidize methane, even when the bulk oxidant $KHSO_5$ was used in large excess (entry 7).

---

(9) Annese, C.; D'Accolti, L.; Fusco, C.; Gandolfi, R.; Eaton, P. E.; Curci, R. *Org. Lett.* **2009**, *11*, 3574.

(10) Oxone, Caroate, triple salt ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).

(11) (a) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699. (b) Murray, R. W.; Singh, M. *Organic Syntheses, Coll. Vol. 9*; Freeman, J. P., Ed.; Wiley: New York, 1998; p 288. (c) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847.

Table 1. Methane Hydroxylation by Dimethyldioxirane (**1a**) and by Methyl(trifluoromethyl)dioxirane (**1b**)[a]

$$CH_4 + \mathbf{1a,b} \longrightarrow CH_3OH + R(CH_3)C{=}O$$

entry	oxidant	$[CH_4]_o$, mM	[oxidant]$_o$, mM	ox/CH_4, Ratio [b]	solvent	temp, °C	reaction time, h	conv,[c] %	$[CH_3OH]$,[d] mM
1	TFDO (**1b**)	—[e]	144	—	Acetone	0	24	—[f]	100
2	TFDO (**1b**)	62	62	1.00	Acetone	−10	24	15.0	9
3	TFDO (**1b**)	30	79	2.5	H_2O	3	24	7.0	2.1
4	DMDO (**1a**)	26	53	2.0	H_2O/Acetone[g]	3	72	5.0	1.3
5	TFDO (**1b**) *in situ*[h]	6	126	20	H_2O	2−5	24	15.0	0.9
6	DMDO (**1a**) *in situ*[i]	8	168	20	H_2O	2−5	24	<2	0.2
7	$KHSO_5$[j]	13	630	48	H_2O	2−5	24	—	—

[a] Unless noted otherwise, reactions were carried out in a sealed flask under CH_4 gas. The amount of CH_4 introduced was established using a constant pressure gas buret at ca. 1 atm. Initial peroxide concentrations were determined by iodometry and/or by a reported GC method (ref 7). [b] Initial concentration ratio of isolated dioxirane (or of $KHSO_5$ bulk oxidant) to CH_4. [c] Methane conversion was estimated based on of the amount of CH_3OH formed. [d] Determined by calibrated GC. [e] Methane gas 2.5 atm, 50 mL pressure vessel containing 3 mL of 0.7 M TFDO in 12 mL of acetone. [f] In this experiment, performed with CH_4 gas excess, the percent conversion was ca. 70%, as determined on the basis of dioxirane limiting reagent; however, concurrent peroxide decomposition over the long reaction time (ref 12) might contribute to an overestimate of the conversion magnitude. [g] Solvent H_2O/acetone 1.5:1. [h] Dioxirane (**1b**) generated *in situ* by TFP/caroate 1:2, aqueous solution pH 7.5−8.0. [i] DMDO (**1a**) generated *in situ*, acetone/caroate 1:1, aqueous solution pH 7.5−8.0. [j] Caroate salt and no ketone, aqueous solution pH 7.5−8.0.

In view of the high C−H bond energy of methane (104 kcal/mol, 435 kJ/mol), its lower rate of oxidation with respect to the ease of dioxirane hydroxylation of unactivated tertiary and secondary carbon−hydrogen bonds in alkanes is hardly surprising. In fact, theoretical calculations provide an estimate of the activation barriers in the gas phase for the oxidation of methane, propane, and isobutane with DMDO as 44.2, 30.3, and 22.4 kcal/mol, respectively.[13]

Concerning the *in situ* method, reactions carried out with TFDO take place with adequate methane conversion. In this case, the recyclability and stable activity of the ketone catalyst could be assessed. In fact, we found that recharging the spent reaction mixture with more methane and bulk $KHSO_5$ oxidant results in additional methanol production.

The potential of the caroate/ketone system appears significant for its practical applications. Indeed, with this method the ketone is not appreciably consumed, since it simply acts as a catalyst to activate the inexpensive caroate oxidant. Covalent attachment of the trifluoromethyl ketone moiety to a solid matrix[14] might provide the additional advantage of easy recycling of the catalyst. Thus, further work seems appropriate to achieve this goal.

In our view, the direct conversion of methane to methanol under mild conditions described herein merits its further exploration. Remarkably, it does not involve costly catalysts and elaborate multistep procedures. It is noteworthy since the rich deposits of methane natural gas and methane hydrates represent a huge source of materials and energy.[15]

Acknowledgment. Financial support by the Ministry of Education of Italy (MIUR, Grant PRIN 2008) and by the Italian National Research Council (CNR, Rome) is gratefully acknowledged. Thanks are also due to Dr. J. Ciabattoni for helpful discussions.

Supporting Information Available. Experimental procedures, sample GC runs, ^1H and ^{13}CNMR characterization data of reaction mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(12) Curci, R.; Dinoi, A.; Fusco, C.; Lillo, M. A. *Tetrahedron Lett.* **1996**, *37*, 249.

(13) Glukhovtsev, M. N.; Canepa, C.; Bach, R. D. *J. Am. Chem. Soc.* **1998**, *120*, 10528.

(14) For instance, see: Song, C. E.; Lim, J. S.; Kim, S. C.; Lu, K.-J.; Chi, D. Y. *Chem. Commun.* **2000**, 2415.

(15) (a) Sloan, E. D., Jr.; Koh, C. A. *Clathrate Hydrates of Natural Gases*, 3rd ed.; CRC Press-Taylor and Francis: Boca Raton, FL, 2008. (b) Milkov, A. V. *Earth Sci. Rev.* **2004**, *66*, 183.