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Mild, Single-Pot Hydrocarboxylation of Gaseous Alkanes to Carboxylic Acids in Metal-Free and Copper-Promoted Aqueous Systems

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Abstract: A direct, selective and highly efficient method has been developed for the hydrocarboxylation of C_n gaseous alkanes into C_{n+1} carboxylic acids, in aqueous acid-solvent-free medium at low temperatures. The approach is based on a metal-free or copper-promoted reaction of ethane, propane or *n*-butane with carbon monoxide and water, in a H_2O/MeCN medium at 50–60 °C, in the presence of potassium peroxodisulfate. The effects of various reaction parameters, such as the absence or presence of a copper promoter, solvent composition, temperature, time, CO and alkane pressure, were studied. A free radical mechanism was confirmed by radical trap experiments involving acyl radical formation, oxidation and subsequent hydroxylation by water. Remarkable yields (based on alkane) of carboxylic acids in the 34–41 % range were achieved even in the metal-free systems, although in the presence of a tetracopper(II) triethanolaminate derived promoter they reach superior values of 58 and 87 % for the hydrocarboxylations of propane and *n*-butane, respectively; in these cases, branched isobutyric and 2-methylbutyric acids were the predominant products. From a green perspective, important features of the present alkane hydrocarboxylations include the exceptional metal-free, mild and acid-solvent-free reaction conditions, the operation in aqueous medium with a rare hydroxylating role of water, with high selectivities, and yields of carboxylic acids. Taken together, these conditions correspond to the mildest and the most efficient method so far reported for the oxidative functionalisation of gaseous alkanes.

Keywords: alkanes · C−H activation · carboxylation · carboxylic acids · copper

Introduction

As the main components of natural gas, light alkanes are abundant and potentially cheap carbon raw materials for added value organic chemicals.[1] However, the high inertness of gaseous alkanes prevents their broad application in the direct syntheses of oxygenated products, and therefore, they are mainly used as fossil fuels or, under drastic conditions involving power-consuming processes (cracking, dehydrogenation and reforming), converted into olefins that are common intermediates in large-tonnage organic synthesis.[1,2] Hence, the search for single-pot, mild and environmentally benign methods of oxidative functionalisation of alkanes constitutes a challenging problem of modern chemistry.[1,3]

In spite of the sweeping development of green chemistry in recent years, its application to alkane-based processes is rather limited,[4] which is primarily due to the unreactive character of the C−H and C−C bonds in alkanes. Thus, in most cases,[1,3] the implementation of relatively mild and selective transformations of light alkanes requires the presence of metal catalysts (commonly bearing precious metals), and the use of strongly acidic reaction media, typically concentrated trifluoroacetic[5,6] or sulfuric[7] acid, or a superacid.[8] Therefore, from a green perspective, there is a strong demand for potential metal-free,[9] acid-solvent-free and/or aqueous medium alternatives[10] of single-pot alkane functionalisation, which are topics of high significance that still remain very poorly developed.

Among the useful organic molecules that can be obtained directly from gaseous alkanes, low aliphatic C_3–C_5 carboxylic acids are important commodity chemicals that are in increasing demand and are used in a wide variety of applications.[2] Their large-scale production is mainly based on the carbonylation of ethylene, oxidation of propanal or naphtha (for propionic acid), liquid-phase oxidation of butyraldehydes (for butyric acids), and carbonylation of olefins or al-

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cohols (for C_5 acids).[2] However, there are still a number of general limitations of those methods from both environmental and cost perspectives, including: 1) the common use of raw materials that are considerably more expensive than alkanes and require prior production; 2) the required multistage transformations, and the need for harsh reaction conditions and expensive metal catalysts; and 3) the low product yields and/or poor selectivity and complex workup.

In pursuit of our general line of research on various metal-catalysed oxidative transformations of alkanes under mild conditions,[6,11,12] we have preliminarily communicated[12a] a novel, efficient and cleaner route for the selective and single-pot synthesis of carboxylic acids from alkanes, which has been further extended to a detailed investigation of cycloalkanes.[12b] This route is based on the hydrocarboxylation reaction of an alkane with carbon monoxide and water in the presence of peroxodisulfate oxidant. In contrast to state-of-the-art alkane carboxylation methods,[5,6] the present approach does not require absolute trifluoroacetic acid (TFA) as a solvent, and proceeds efficiently in aqueous acid-solvent-free medium (H_2O/MeCN mixed solvent), at mild temperatures (50–60 °C) and even in the absence of any metal catalyst.

Hence, the general objective of the current study was the detailed investigation and optimisation of the hydrocarboxylation of C_n gaseous alkanes (ethane, propane and *n*-butane) to the corresponding C_{n+1} carboxylic acids, by studying the influence of a variety of experimental conditions (i.e., the absence or presence of a metal promoter, solvent composition, temperature, time, and relative amounts of substrate and carbon monoxide). Although the method we are reporting still has some environmental limitations, its significance in a green context with respect to prior work on alkane carboxylations[5,6,13] and on mild alkane transformations in general[1,3,7] consists of the following features: 1) the use of an aqueous acid-solvent-free medium; 2) the possibility of operating under metal-free conditions; 3) the very mild temperatures; 4) the rather high efficiency and selectivity, and 5) the useful application of water as a relevant reagent that provides the main source of the OH group in the carboxylic acid product.

Results and Discussion

Metal-free versus copper-promoted hydrocarboxylation of alkanes: The hydrocarboxylations of gaseous alkanes were undertaken in stainless steel autoclaves by treating an alkane with CO, water and potassium peroxodisulfate at low temperature (typically 50–60 °C) in neutral H_2O/MeCN medium, either in the absence (metal-free process) or in the presence of a copper promoter (copper-promoted process) (Scheme 1). Hence, ethane was directly converted into propionic acid, propane into isobutyric (major product) and butyric acids, and *n*-butane was transformed into 2-methylbutyric (major product) and valeric acids. Surprisingly, these mild and selective transformations of inert alkanes proceed rather efficiently in metal-free systems, wherein a crucial role is played by the active radical sulfate $SO_4^{\bullet-}$ (known as an active single electron-transfer oxidant),[14] generated upon thermolysis of peroxodisulfate. It should be stressed that the metal-free carboxylations also proceed with the same efficiency in a Teflon reactor, thus confirming that the reactions are not promoted by the reactor metal wall.

$$R{-}H + CO + H_2O + S_2O_8^{2-} \xrightarrow[50\text{–}60\ ^\circ C]{H_2O/MeCN \ (Cu\ promoter)} R{-}COOH \ + \ 2HSO_4^-$$

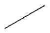
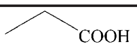
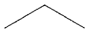
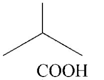
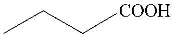
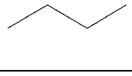
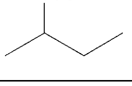
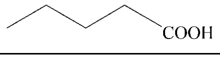
R = Et, Pr, *n*Bu

Scheme 1. Hydrocarboxylation of C_n alkanes to the corresponding C_{n+1} carboxylic acids in H_2O/MeCN medium.

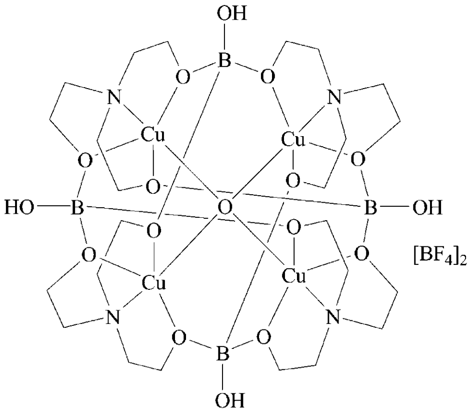
Since the effectiveness of various metal-free oxidative transformations can be improved by the presence of a metal promoter (or metal catalyst),[9,12] we used hydrosoluble tetracopper(II) triethanolaminate derivative $[O\subset Cu_4\{N(CH_2CH_2O)_3\}_4(BOH)_4][BF_4]_2$ (**1**) for this purpose. This promoter has previously been shown to display the highest efficiency in such alkane carboxylations,[12] and is also a remarkable catalyst for the oxidation of cycloalkanes and benzyl alcohols.[15] Selected results obtained for the metal-free and copper-promoted hydrocarboxylation of gaseous alkanes are given in Table 1, and briefly discussed below.

The metal-free hydrocarboxylation of ethane (Table 1, entry 1) leads to the formation of propionic acid in 34 % yield (all yield values in this paper are rounded off and are

Table 1. Metal-free versus copper-promoted hydrocarboxylation of gaseous alkanes to carboxylic acids in H_2O/MeCN medium.[a]

Entry	Alkane	Carboxylic acid product	Total yield [%][b] (bond selectivity) Metal free	Total yield [%][b] (bond selectivity) Copper promoted[c]
1			33.7[d]	17.1[d]
2		 	41.0[e] (1°/2° = 1:21)	58.3[e] (1°/2° = 1:28)
3		 	34.1[d] (1°/2° = 1:24)	86.7[e] (1°/2° = 1:35)

[a] Selected results (for more assays, see Tables 2, 3 and 4), major product is indicated first; reaction conditions (unless stated otherwise): p(alkane) = 1.0, 1.0 and 0.75 atm (1 atm = 0.266 mmol) for C_2H_6, C_3H_8 and n-C_4H_{10}, respectively; p(CO) = 10.0 atm; $K_2S_2O_8$ = 1.5, 1.0 and 1.0 mmol for reactions with C_2H_6, C_3H_8 and n-C_4H_{10}, respectively; H_2O (3 mL)/MeCN (3 mL); 50 °C (for n-C_4H_{10}) or 60 °C (for C_2H_6 and C_3H_8); 6 h in an autoclave (13.0 mL capacity). [b] Total yield (moles of all carboxylic acids/100 moles of alkane) determined by GC analysis; whenever applicable, selectivity parameters are indicated in brackets: 1°/2° stand for bond selectivity, with respect to the relative normalised reactivities of hydrogen atoms at primary and secondary carbon atoms of alkanes. [c] In the presence of compound **1** (4.0 μmol). [d] 17 h. [e] H_2O (2 mL)/MeCN (4 mL).



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based on alkane). In the corresponding copper-containing system, the yield drops to approximately half, which points to an eventual inhibiting effect of compound **1** in the hydrocarboxylation of ethane, conceivably due to competitive ethane oxidation reactions that only occur in the presence of the metal catalyst. In fact, the yields of oxidation products (alcohols and ketones) in the hydrocarboxylation of cyclohexane are increased in the presence of **1**.[12b]

In contrast to studies with ethane, the promoting role of **1** was evident in the reactions with propane and *n*-butane; in these cases, the yields of the corresponding carboxylic acids of 58 and 87 %, respectively (Table 1, entries 2 and 3), were higher than those obtained in the metal-free hydrocarboxylation (41 and 34 %, respectively).

The reactivities of the hydrogen atoms at secondary carbon centres in propane and *n*-butane are dominant, leading to the formation of isobutyric and 2-methylbutyric acids as the main products, respectively. This is more pronounced in the copper-promoted systems than in the metal-free versions, as exemplified by the higher bond selectivity parameters (1°/2°) of 1:35 versus 1:24, respectively, in the hydrocarboxylation of *n*-butane (entry 3). The bond selectivity parameter 1°/2° refers to the normalised (for the relative number of hydrogen atoms) reactivities of hydrogen atoms at primary and secondary carbon atoms of the alkanes.

Furthermore, a very high selectivity towards the formation of carboxylic acids, under both metal-free and Cu-promoted systems, was observed for all the alkanes tested; generation of alcohols and ketones as byproducts of partial alkane oxidations did not exceed 1 % of the overall yield.

The achieved yields of carboxylic acids (34–87 %) are remarkable, considering the high degree of inertness of gaseous alkanes, the very mild reaction conditions, the use of aqueous medium and the possibility of operating in metal-free systems. In this regard, it should be mentioned that some transformations of gaseous alkanes into carboxylic acids in water have previously been reported,[13] including: 1) metal-free[13a] and Rh-catalysed[13b] carbonylations of methane and ethane in $H_2O/CO/K_2S_2O_8$ (or O_2) systems, and 2) vanadium-catalysed carboxylations of methane in the H_2O/CO/air system.[13c] However, all these processes exhibited low efficiencies in terms of carboxylic acid yields, which did not exceed 0.4 % relatively to the alkane.[13]

More data on alkane hydrocarboxylations, including the effects of solvent composition, temperature, time, and CO and alkane pressures, are summarised in Tables 2, 3 and 4 and Figure 1, and are discussed below, particularly regarding the reactions with propane as a model substrate.

Hydrocarboxylation of ethane to propionic acid: Due to the presence of only primary carbon atoms, ethane appears to be the least reactive alkane towards hydrocarboxylation, apart from methane, for which the attempted conversion to acetic acid has so far been unsuccessful. Hence, typical yields of propionic acid after 6 h reaction time lie in the 8–10 % range (Table 2, entries 1–3) when using 10 atm of ethane, 20–30 atm of CO and the optimal H_2O/MeCN (3 mL/3 mL) solvent composition. The reaction does not occur either in only water or acetonitrile (Table 2, entry 6), and is also less efficient in the presence of an excess of either of the solvents (entries 5 and 4). Higher yields of propionic acid (up to 34 %) can be attained by lowering the ethane pressure to 1 atm and by prolonging the reaction time to 17 h (Table 2, entry 9).

Table 2. Hydrocarboxylation of ethane to propionic acid.[a]

Entry	$p(C_2H_6)$ [atm]	p(CO) [atm]	t [h]	Solvent H_2O/ MeCN [mL]	$K_2S_2O_8$ [mmol]	Propionic acid [%][b]
1	10	30	6	3:3	3.0	8.0
2	10	30	6	3:3	1.5	9.4
3	10	20	6	3:3	2.0	9.7 (9.9)[c]
4	10	20	6	2:4	2.0	4.7 (6.2)[c]
5	10	20	6	4:2	2.0	0.9 (6.4)[c]
6	10	20	6	6:0 (or 0:6)	2.0	0
7	5	30	6	2:4	1.5	2.0
8	3	10	17	3:3	1.5	5.0
9	1	10	17	3:3	1.5	17.1 (33.7)[c]
10[d]	10	20	6	3:3	2.0	5.3

[a] Reaction conditions (unless stated otherwise): 60 °C, in an autoclave (13.0 mL capacity), in the presence of compound **1** (4.0 μmol). [b] Yield (moles of propionic acids/100 moles of ethane) of propionic acid determined by GC analysis. [c] Yield in brackets was obtained in the absence of compound **1** (metal-free system). [d] $Ca[V\{ON(CH_2COO)_2\}_2]$ (4.0 μmol) was used instead of **1**.

As mentioned above, better yields of propionic acid are typically observed in the metal-free systems; compound **1** produces an inhibiting effect, depending on the reaction conditions (Table 2, entries 3–5, 9). It should be noted that inhibition behaviour is also displayed by $Ca[V\{ON(CH_2COO)_2\}_2]$ (Table 2, entry 10), which is one of the most efficient catalysts for ethane carboxylation in TFA medium.[6a]

Propionic acid appears to be the only product of the ethane hydrocarboxylation, since neither the partial oxidation of ethane, nor the conversion of acetonitrile into acetic acid, were detected. The acetonitrile solvent was inert towards carboxylation under the reaction conditions, since no propionic acid formation was observed upon repeating the reaction in the absence of ethane (blank test).

Hydrocarboxylation of propane to butyric acids: The hydrocarboxylation of propane proceeded more efficiently than that of ethane, leading to substantial yields of butyric acids, both in the metal-free and copper-promoted processes (overall yields up to 41 and 58 %, respectively). Isobutyric acid was always the predominant product, with the yields of butyric acid typically being one order of magnitude lower. The reactions were dependent on a variety of experimental factors, which are shown in Figure 1 and Table 3.

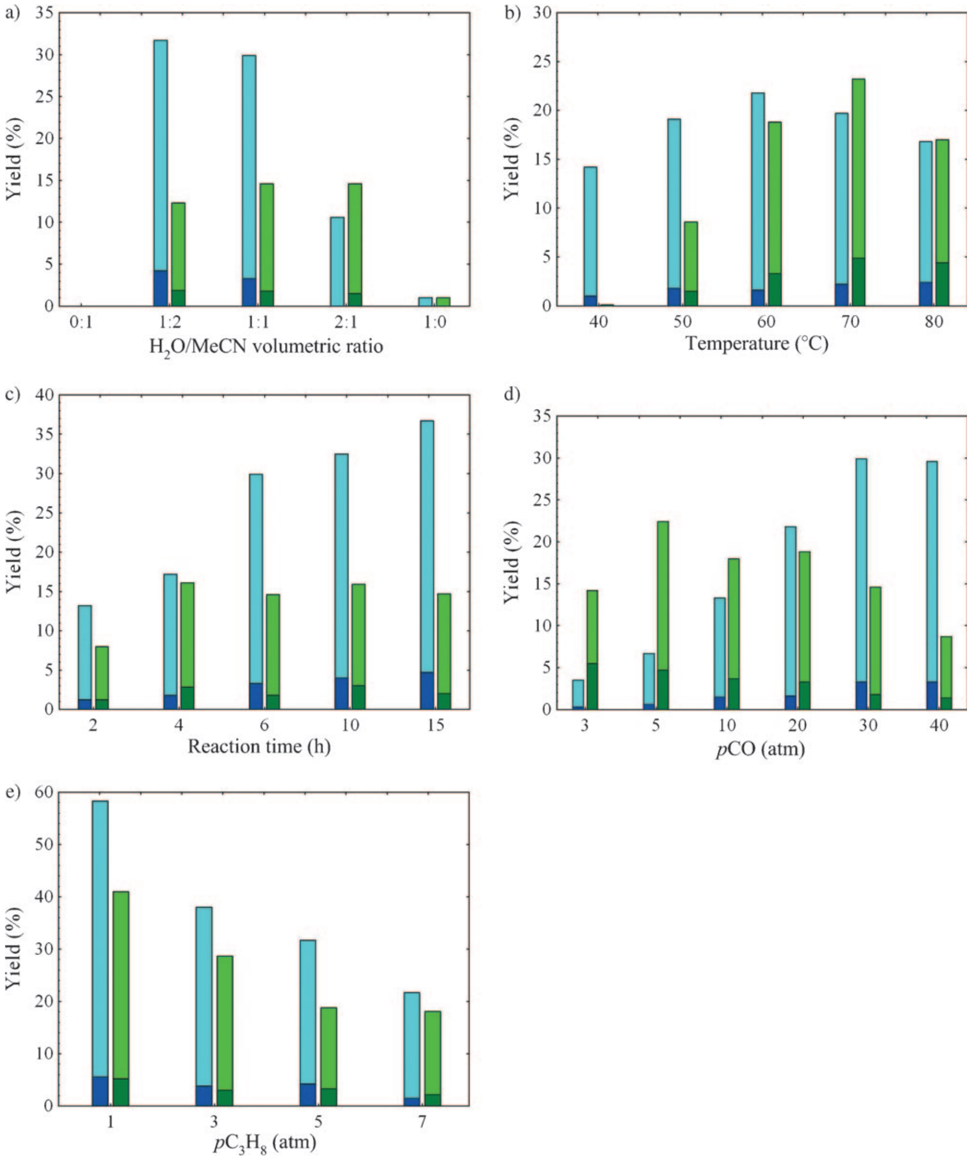


Figure 1. Effects of a) solvent composition, b) temperature, c) reaction time, and pressures of d) carbon monoxide and e) propane on the yields of isobutyric (light green/blue coloured) and butyric (dark green/blue coloured) acids in the hydrocarboxylation of C_3H_8. Green (right) and blue (left) bars correspond to the metal-free and copper-promoted processes, respectively. Typical reaction conditions (except for the varying parameter) are those given in Table 3, entry 5 for diagrams (a)–(d); entries 1, 9, 12, 14 (Cu promoted) or 2, 4, 11, 14 (metal free) for diagram (e).

The solvent composition was a very important reaction parameter in the hydrocarboxylation of propane (Figure 1 a). Unfortunately, the reaction did not proceed appreciably (1 % products yield) in only water, which would be the ideal solvent from both environmental and cost perspectives.[4a,d,10,16] Neither could butyric acids be obtained when using acetonitrile as the sole solvent (Figure 1 a). However, the mixed H_2O/MeCN solvent appears to be remarkably suitable; use of this solvent system led to 32 and 30 % overall yields of butyric acids, for $p(C_3H_8) = 5$ atm and $p(CO) = 30$ atm, in the Cu-promoted systems at the optimal 1:2 and 1:1 H_2O/MeCN volumetric ratios, respectively (Figure 1 a, Table 3, entries 9 and 5). When the reaction was undertaken with a double excess of water relative to acetonitrile, the corresponding yield fell to 11 %. In the metal-free systems, the overall yields of butyric acids were similar (12–14 %) at different solvent compositions (2:1 to 1:2 H_2O/MeCN range). The two solvents play essential functions: acetonitrile dissolves the organic species, whereas water is required to solubilise the peroxodisulfate oxidant and, most importantly, to provide the main source of the hydroxyl group for the carboxylic acid product. For the first time, this remarkable carboxylating role of water was recently confirmed by us on the basis of experiments with $H_2{}^{18}O$.[12a]

Although the mixed H_2O/MeCN solvent system can be easily recycled and is far greener and cheaper than the absolute trifluoroacetic acid, which is used as the conventional solvent for the alkane carboxylations,[5,6] the presence of acetonitrile still constitutes a drawback from an environmental perspective. However, one should mention that various water/organic solvent mixtures are typically less noxious than the pure organic solvents.[17] Replacement of acetonitrile with acetone has been attempted in the propane hydrocarboxylation, but resulted in a modest overall yield of 10 versus 30 % for the H_2O/MeCN system (Table 3, entry 15 vs. 5). Moreover, the use of H_2O/

Table 3. Copper-promoted and metal-free hydrocarboxylation of propane to butyric acids.[a]

Entry	$p(C_3H_8)$ [atm]	p(CO) [atm]	t [h]	H_2O/MeCN [mL]	Carboxylic acid yield [%][b] Isobutyric	Butyric	Total	Bond selectivity 1°/2°[c]
1	7	30	6	2:4	20.2	1.5	21.7	1:40
2	7	20	6	3:3	(15.9)	(2.2)	(18.1)	(1:22)
3	5	10	6	3:3	11.8 (14.3)	1.5 (3.7)	13.3 (18.0)	1:24 (1:12)
4	5	20	6	3:3	20.2 (15.5)	1.6 (3.3)	21.8 (18.8)	1:38 (1:14)
5	5	30	6	3:3	26.6 (12.7)	3.3 (1.8)	29.9 (14.5)	1:24 (1:21)
6	5	40	6	3:3	26.4 (7.3)	3.3 (1.4)	29.6 (8.7)	1:24 (1:16)
7	5	30	10	3:3	28.5	4.0	32.5	1:21
8	5	30	15	3:3	32.0 (12.7)	4.7 (2.0)	36.7 (14.7)	1:20 (1:19)
9	5	30	6	2:4	27.5 (10.4)	4.2 (1.9)	31.7 (12.3)	1:20 (1:16)
10	5	30	6	4:2	10.6 (13.1)	0 (1.5)	10.6 (14.6)	– (1:26)
11	3	20	6	3:3	(25.7)	(3.0)	(28.7)	(1:26)
12	3	30	6	2:4	34.2	3.8	38.0	1:27
13[d]	3	10	6	2:4	27.6	3.1	30.7	1:27
14[d]	1	10	6	2:4	52.7 (35.8)	5.6 (5.2)	58.3 (41.0)	1:28 (1:21)
15[e]	5	30	6	3:3	9.0	1.2	10.2	1:23
16[f]	5	30	6	3:3	20.4	3.2	23.4	1:19
17[g]	5	20	6	3:3	(0.0)	(0.0)	(0.0)	(–)

[a] Yield and bond selectivity values in brackets correspond to metal-free systems; selected results (additional assays are given in Figure 1); reaction conditions (unless stated otherwise): $K_2S_2O_8 = 1.5$ mmol, 60 °C, in an autoclave (13.0 mL capacity), in the presence of compound **1** (8.0 μmol). [b] Yield (moles of carboxylic acid/100 moles of propane) determined by GC analysis. [c] Bond selectivity parameter 1°/2° corresponds to the relative normalised reactivities of hydrogen atoms at primary and secondary carbon atoms in propane. [d] Compound **1** (4.0 μmol), $K_2S_2O_8 = 1.0$ mmol. [e] Acetone (3 mL) was used instead of MeCN. [f] Ca[V{ON(CH$_2$COO)$_2$}$_2$] (8.0 μmol) was used instead of **1**. [g] Reaction performed in the presence of $CBrCl_3$ (1.0 mmol) leading to the formation of 2-bromopropane (12.2 %) and 1-bromopropane (4.9 %) as the only observed products.

EtOH or $H_2O/CHCl_3$ solvent compositions resulted in the formation of only traces of isobutyric acid. The poor results obtained when using acetone or ethanol as the second component of the solvent mixture can be associated with their increased reactivity (compared to MeCN) towards oxidation, which can compete with the carboxylation reaction. The unsuitability of chloroform in the reaction can be due to solubility problems (heterogeneous system) and its radical trap behaviour (see the discussion of experiments with $CBrCl_3$ below).

As can be seen from Figure 1 b, the temperature is also an important reaction parameter. Hence, for the Cu-promoted system, the overall yield of butyric acids (14 %) obtained at 40 °C can be considered rather high, taking into account the inertness of this gaseous alkane. However, the hydrocarboxylation is more efficient with a slight increase in the temperature, attaining the optimal yield values at 60 °C. Interestingly, the metal-free system requires about 10 °C higher temperatures to reach activities similar to that of the Cu-promoted system. Thus, only traces of isobutyric acid are formed at 40 °C in the metal-free reaction, whereas an overall yield of 8 % is observed at 50 °C, which increases to 23 % at the optimal temperature of 70 °C (Figure 1 b). Further increases in temperature led to a gradual drop in yield as a result of thermal decomposition of the peroxodisulfate.[12a,14]

The accumulation of products was already observed after 2 h of reaction (Figure 1 c). However, in a metal-free system, a slightly longer reaction time of 4 h was typically required to achieve the optimum value (16 %) of overall yield, which remained almost invariable beyond this time. In contrast, in the copper-promoted system, the overall yield of butyric acids gradually increased from 13 to 37 % on extending the reaction time from 2 to 15 h.

Although alkane carboxylations in TFA are known to proceed even in the absence of CO (with TFA acting then as the carbonylating agent[6]), the hydrocarboxylation of propane in H_2O/MeCN medium does not proceed to any extent unless CO is added, because no other carbonylating reagent is present. Carbon monoxide is typically introduced into the reaction mixture in some excess relative to propane to generate the highest product yields. As for the reaction time, changes in the CO pressure affect the metal-free and copper-promoted hydrocarboxylations differently (Figure 1 d). Thus, for the metal-free reaction, the highest overall yield of 23 % was achieved at low CO pressure (5 atm); higher pressures led to a reduction in yield. In the Cu-promoted process, an increase of p(CO) led to a gradual increase in yield, reaching the optimal value of 30 % at 30 atm of CO. Although replacing CO with CO_2 as an alternative carboxylating agent would be very desirable from an environmental viewpoint, all such attempts have so far been unsuccessful.

Propane pressure also has a considerable influence on the reaction (Figure 1 e) as it determines the amount of substrate in the reaction mixture. Hence, a clear trend of yield growth on lowering the propane pressure can be detected in both metal-free and Cu-promoted processes. The highest yields of butyric acids of 41 and 58 %, respectively, were thus achieved at $p(C_3H_8)$ of 1 atm. Nevertheless, the product yields were also significant at elevated pressures of propane (Table 3).

The observed bond selectivity parameter 1°/2° is indicative of the predominant reactivity of the methylene over the methyl protons in propane (and is suggestive of a radical mechanism); this is also dependent on a variety of reaction factors and, in particular, on the presence of the copper promoter (Table 3). The typical 1°/2° parameter values lie in the 1:20 to 1:28 range for the Cu-promoted systems, whereas they are generally about one-third smaller in the metal-free reactions (i.e., 1°/2° ratio of 1:12 to 1:19). Such a difference in bond selectivity suggests that compound **1** not only promotes the hydrocarboxylation, but also affects the mechanistic pathway and the product distribution pattern.

For comparison, we also tested Ca[V{ON(CH$_2$COO)$_2$}$_2$] as a promoter; this resulted in a slightly inferior yield and selectivity (23 %, 1°/2° = 1:19) than when the reaction was performed in the presence of compound **1** (30 %, 1°/2° = 1:24) (Table 3, entry 16 vs. 5). Interestingly, the bond selectivities given above are significantly higher (1°/2° ratio 1:3 to 1:7) than those obtained in the V-catalysed carboxylation of propane in TFA.[6d] Moreover, the latter reaction generated a considerable amount (up to 8 %) of acetic acid through C−C bond cleavage and oxidation processes; such side reactions were not observed under the conditions developed in the present work.

Hydrocarboxylation of *n*-butane to 2-methylbutyric and valeric acids: In general, the hydrocarboxylation of *n*-butane exhibits features similar to those observed in the case of propane and, thus, is not discussed in much detail. Butane hydrocarboxylation at the secondary carbon atoms is even more preferable, as attested to by the superior bond selectivity 1°/2°, which lies in the 1:33 to 1:54 and 1:17 to 1:24 ranges for the Cu-promoted and metal-free systems, respectively (Table 4). Hence, 2-methylbutyric acid is always the predominant product, whereas the amount of valeric acid formed is relatively minor, not exceeding 3.6 % yield (Table 4, entry 9). Considerable amounts of products can be obtained even in the metal-free systems (Table 4, entries 2 and 8), although the Cu-promoted reactions always resulted in superior yields. The effect of CO pressure was studied (Table 4, entries 1–5), revealing a maximum overall yield of 51 % at a p(CO) of 15 atm (Table 4, entry 2). When the effect of time was investigated (Table 4, entries 2 and 6–8), a considerable accumulation of products was found to occur after 6 h of reaction (entry 2), although the highest yields of 34 (metal free) and 80 % (Cu promoted) were attained after 17 h (entry 8). However, in the Cu-promoted system, an even higher yield of 87 % could be obtained after 6 h, providing the reaction was performed in a solvent composed of a double excess of acetonitrile over water (Table 4, entry 9). In contrast, a much lower yield (28 %) was obtained with a 2:1 water/acetonitrile volumetric ratio (Table 4, entry 10).

Attempts to replace **1** with the vanadium-containing compound, $Ca[V\{ON(CH_2COO)_2\}_2]$, resulted in yields almost identical to those obtained in the metal-free system (Table 4, entries 12 and 2). Although the tetracopper(II) complex **1** exhibits a significant promoting effect on butane hydrocarboxylation, its substitution for a simple copper salt, $Cu(NO_3)_2{\cdot}2.5\,H_2O$, resulted in a strong inhibiting effect, leading to an overall product yield of only 14 % versus 25 % in the metal-free system (Table 4, entries 11 and 2). This fact indicates the particular relevance of the N,O-ligands and their intricate arrangement in **1**. Apart from the high activity of **1**, the application of this compound as the preferable metal promoter is also favoured by its solubility in water, its high stability and its facile self-assembly synthesis in aqueous medium from readily available and relatively inexpensive chemicals.[15a,b] However, further exploration of alkane hydrocarboxylations cannot be limited to use of the promoter **1**, and other water-soluble transition-metal complexes[11a,c,18] should also be tested.

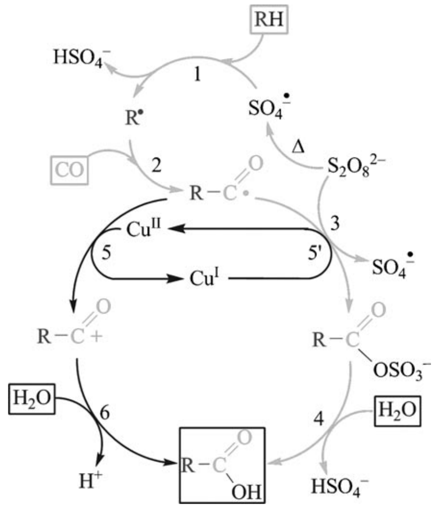
Reaction mechanism: Background knowledge accumulated on the carboxylation of alkanes, both in TFA[6] and in H_2O/MeCN[12] media, supports a free radical mechanism. Hence, based on literature and experimental data, tests with radical traps and ^{18}O-labelled water and on theoretical calculations,[12a] the simplified mechanism presented in Scheme 2 is proposed for metal-free and Cu-promoted hydrocarboxylation of gaseous alkanes. The first step involves the generation of a free alkyl radical $R^{\bullet}$, which is formed through hydrogen-atom abstraction from an alkane by the sulfate radical $SO_4^{\bullet -}$ (reaction 1). The latter is derived from the thermolytic and copper-promoted (when in the presence of **1**) decomposition of $K_2S_2O_8$.[6a–c,13a,14a] It is important to mention that almost quantitative transformation of potassium peroxodisulfate into $KHSO_4$ (reaction 1) takes place in the hydrocarboxylation reactions. In fact, upon cooling the reaction mixtures, this salt crystallises and can be easily separated by filtration; this salt can potentially be reconverted into $K_2S_2O_8$ through established electrochemical processes.[19]

Table 4. Copper-promoted and metal-free hydrocarboxylation of *n*-butane to 2-methylbutyric and valeric acids.[a]

Entry	p(CO) [atm]	t [h]	Carboxylic acid yield [%][b] 2-Methylbutyric	Valeric	Total	Bond selectivity 1°/2°[c]
1	5	6	14.3	0.4	14.7	1:54
2	10	6	43.8 (23.6)	1.7 (1.7)	45.5 (25.3)	1:39 (1:21)
3	15	6	48.9	1.9	50.8	1:39
4	20	6	39.8	1.6	41.5	1:37
5	30	6	4.9	0.2	5.1	1:37
6	10	2	1.3 (0)	0 (0)	1.3 (0)	–
7	10	4	10.9 (9.3)	0.5 (0.8)	11.4 (10.1)	1:33 (1:17)
8	10	17	77.8 (32.1)	2.4 (2.0)	80.2 (34.1)	1:49 (1:24)
9[d]	10	6	83.1 (14.3)	3.6 (0.9)	86.7 (15.2)	1:35 (1:24)
10[e]	10	6	26.8	0.9	27.7	1:45
11[f]	10	6	12.9	1.3	14.2	1:15
12[g]	10	6	21.2	2.4	23.6	1:13
13[h]	10	6	3.3 (2.8)	0.1 (0.1)	3.3 (2.9)	1:50 (1:42)

[a] Yield and bond selectivity values in brackets correspond to metal-free systems; reaction conditions (unless stated otherwise): $p(C_4H_{10}) = 0.75$ atm (1.0 atm = 0.266 mmol), $K_2S_2O_8 = 1.0$ mmol, H_2O (3 mL)/MeCN (3 mL), 50 °C, in an autoclave (13.0 mL capacity), in the presence of compound **1** (4.0 μmol). [b] Yield (moles of carboxylic acid/100 moles of *n*-butane) determined by GC analysis. [c] Bond selectivity parameter 1°/2° corresponds to the relative normalised reactivities of hydrogen atoms at primary and secondary carbon atoms in *n*-butane. [d] H_2O (2 mL)/MeCN (4 mL). [e] H_2O (4 mL)/MeCN (2 mL). [f] $Cu(NO_3)_2 \times 2.5H_2O$ (4.0 μmol) was used instead of **1**. [g] $Ca[V\{ON(CH(CH_3)COO)_2\}_2]$ (4.0 μmol) was used instead of **1**. [h] Reaction performed in the presence of $CBrCl_3$ (1.0 mmol) leading to the formation of 2-bromobutane [20.1 % (Cu promoted) and 10.0 % (metal-free)] and 1-bromobutane [1.0 % (Cu promoted) and 0.5 % (metal free)].

The involvement of alkyl radicals was supported by perform-



Scheme 2. Proposed simplified mechanism for the hydrocarboxylation of gaseous alkanes in H_2O/MeCN medium.

ing the hydrocarboxylations in the presence of $CBrCl_3$ as a C-centred radical trap. Under these conditions, full suppression of carboxylic acid formation was observed in the metal-free reaction with propane (Table 3, entry 17 vs. 4), with the appearance of 2-bromopropane (12%) and 1-bromopropane (5%) products (entry 17). Similar behaviour was observed in the hydrocarboxylation of *n*-butane, in which the overall carboxylic acid yields declined from 25 and 46% (metal-free and Cu-promoted systems, respectively) to 3% in the presence of $CBrCl_3$ (Table 4, entry 2 vs. 13). In this case, 2-bromobutane was formed as the major product with a yield of either 20 (Cu promoted) or 10% (metal free), whilst the yields of 1-bromobutane did not exceed 1%.

Subsequent carbonylation of the alkyl radical by CO gives an acyl radical $RCO^•$ (Scheme 2, reaction 2) that, upon oxidation by $S_2O_8^{2-}$, forms the acyl sulfate $RC(O)OSO_3^-$ (reaction 3). Hydrolysis of the latter by water (Scheme 2, reaction 4) results in the carboxylic acid product.[12a]

An alternative pathway (Scheme 2, reaction 5) can take place in the copper-promoted process in which **1** can act as an oxidant of the acyl radical (reaction 5). This route involves the Cu^{II}/Cu^I redox couple, and requires $K_2S_2O_8$ to regenerate the Cu^{II} form (Scheme 2, reaction 5′). In this regard, it is worthwhile mentioning that Cu^{II} is particularly effective in the oxidation of C-centred radicals.[14a] The acyl cation RCO^+ thus formed, is hydrolysed, furnishing the carboxylic acid product (Scheme 2, reaction 6). This last reaction occurs through the protonated carboxylic acid $RC(OH)_2^+$ (formed by nucleophilic attack of H_2O on RCO^+), which is deprotonated by water, as supported by theoretical calculations on the corresponding ethyl species.[12a] Hence, the important hydroxylating role of water is reflected in both the metal-free (3→4) and Cu-promoted (5→6) pathways, as confirmed by us[12a] in the course of experiments with $H_2{}^{18}O$, which resulted in the formation of $RCO^{18}OH$ as the main product.

Nevertheless, a less favourable route, in which the formation of the carboxylic acid may occur through the mixed anhydride $RC(O)OSO_3H$ should also be mentioned. This anhydride can be generated by protonation of the acyl sulfate by HSO_4^- or by coupling of RCO^+ with HSO_4^-, and would undergo intramolecular hydrogen transfer with elimination of SO_3, thus leading to the carboxylic acid product.[12a]

Conclusion

The present study shows that even the most inert hydrocarbons (i.e., alkanes) can be selectively and efficiently transformed into useful organic products under mild and relatively environmentally benign conditions, thus extending a green chemistry approach to alkane-based processes. Hence, ethane, propane and *n*-butane are converted into propionic, isobutyric and 2-methylbutyric acids, respectively, as the main products, through single-pot aqueous medium hydrocarboxylation with carbon monoxide, water and potassium peroxodisulfate, representing the mildest and the most efficient method so far reported for the oxidative functionalisation of gaseous alkanes.

The hydrocarboxylations have been optimised by studying the effects of a variety of reaction parameters, allowing remarkably high overall yields (based on alkane) of carboxylic acids, namely, 34% of propionic acid, 58% of butyric acids, and 87% of 2-methylbutyric and valeric acids in the reactions with ethane, propane and *n*-butane, respectively, to be achieved. A significant promoting effect of the water-soluble tetracopper(II) complex **1** was observed in the hydrocarboxylations of propane and *n*-butane, although this compound was found to inhibit the reaction with ethane. Moreover, different bond selectivities have been observed in the metal-free and Cu-promoted reactions, possibly indicating the involvement of distinct steps in the reaction mechanisms. A free radical mechanism is confirmed by tests with a radical trap.

Although the present method still has some environmental limitations (particularly in terms of requiring the use of acetonitrile as a solvent component and peroxodisulfate as an oxidant), it bears a number of remarkably green features in comparison with most of the state-of-the-art methods[1,3,5–9,13] of light-alkane functionalisation. Those features include the exceptional possibility of operating under metal-free conditions at very mild temperatures, in aqueous acid-solvent-free medium and using water as a relevant reagent. The approach also leads to high selectivities and product yields.

This work contributes to the development of environmentally viable alkane functionalisations, however, an in-depth screening of the following improvements should still be undertaken: 1) substitution of $K_2S_2O_8$ for a cheaper and cleaner oxidant (e.g., air, O_2 or H_2O_2), 2) development of an organic-solvent-free reaction medium or replacement of acetonitrile with a less harmful solvent (e.g., bioethanol), and 3) use of CO_2 as a desirable chemical feedstock that can be used as the carboxylating agent instead of CO. Studies that address these and other issues are in progress in our laboratory.

Experimental Section

General methods: All chemicals were obtained from commercial sources and used as received. Compound **1**[15a] and the other tested promoters[20] were prepared according to published procedures. GC analyses were performed with a Fisons Instruments GC 8000 series gas chromatograph with a DB WAX (J&W) capillary column (30 m × 0.25 mm × 0.25 μm; helium carrier gas) and by using Jasco–Borwin v.1.50 software. In some cases, carboxylation products were also identified by GC–MS, ^{1}H and ^{13}C{^{1}H}NMR spectroscopy techniques by using a Trio 2000 Fisons spectrometer with a coupled Carlo Erba (Auto/HRGC/MS) gas chromatograph, and a Varian UNITY 300 NMR spectrometer, respectively.

Alkane hydrocarboxylations: In a typical experiment, the reaction mixtures were prepared as follows: $K_2S_2O_8$ (1.00–2.00 mmol), H_2O (2.0–4.0 mL) and MeCN (2.0–4.0 mL) (typical total solvent volume was 6.0 mL) were added to the metal promoter (optional; 0.0–16.0 μmol, typically 4.0 μmol) contained in a 13.0 mL stainless steel autoclave, equipped with a Teflon-coated magnetic stirring bar. The autoclave was closed and flushed with N_2 three times to remove the air, and pressurised with gaseous alkane (0.75–10.0 atm; typically 10.0, 5.0 or 0.75 atm of ethane, propane or *n*-butane, respectively) and CO (5–40 atm; typically 20 atm). The reaction mixture was stirred for 1–20 h (typically 6 h) at 25–80 °C (typically 50 or 60 °C) using a magnetic stirrer and an oil bath, whereupon it was cooled in an ice bath, degassed, opened and transferred to a flask. Diethyl ether (9.0–11.0 mL) and cycloheptanone (90 μL; GC internal standard) were added. The obtained mixture was vigorously stirred for 10 min, and the organic layer was analysed by GC, revealing the formation of carboxylic acids as the dominant products. In some cases (typically at low CO pressures), the presence of alcohols and ketones as by-products of partial alkane oxidation was also detected, however, their overall yields did not exceed 1 %.

Additional experiments were performed under the typical reaction conditions in the presence of the carbon-centred radical trap $CBrCl_3$, revealing the suppression of carboxylic acid formation, either in the presence or in the absence of the metal promoter.

Blank tests indicated that the metal-free hydrocarboxylations proceed with similar efficacy in a Teflon reactor, thus confirming that the reactions were not promoted by the reactor metal wall. In addition, no generation of acetic or propionic acids from the acetonitrile solvent was detected when the reactions were repeated in the absence of the alkane.

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