Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Reductive Alkylation of Active Methylene Compounds with Carbonyl Derivatives, Calcium Hydride and a Heterogeneous Catalyst

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A one-pot two-step reaction (Knoevenagel condensation - reduction of the double bond) has been developed using calcium hydride as a reductant in the presence of a supported noble metal catalyst. The reaction between carbonyl compounds and active methylene compounds such as methylcyanoacetate, 1,3-dimethylbarbituric acid, dimedone and the more challenging dimethylmalonate, affords the corresponding monoalkylated products in moderate to good yields (up to 83%) with minimal reduction of the starting carbonyl compounds.

Introduction

The development of methodologies to create C-C bonds remains an important research area. Active methylene compounds such as malonates, malononitrile, 1,3-diketones, Meldrum acid or barbituric acid are useful starting materials due to the low pK_a of the methylene protons. The corresponding mono-alkylated compounds are useful synthetic intermediates, for example, for the preparation of pharmaceutical and agrochemical compounds.[1] However, a selective mono-alkylation of an active methylene compound with an electrophilic alkylating reagent in the presence of a base is often challenging to achieve, as such compounds are generally prone to a second addition of the electrophile; as a result, the reaction gives a mixture of mono- and di-alkylated products which are often difficult to separate.

One way to selectively prepare the mono-alkylated product is the reduction of the alkene isolated from a Knoevenagel condensation. The reaction sequence of a Knoevenagel condensation and a subsequent reduction can be performed in one pot, and it is often referred to as the reductive alkylation for a C-C bond formation, which is less widespread than the formation of a C-N bond by a reductive amination.[2] The reductive alkylation can be carried out by a sequential addition of a base then a reductant to avoid the undesired reduction of the starting carbonyl compound (indirect reductive alkylation).[3] This sequential two-step procedure has been described with different base/reductant combinations, such as K_3PO_4/$NaBH_4$,[4] alumina/$NaBH_4$,[5] piperidinium acetate/$NaBH_3CN$,[6] ruthenium-amido complex/ $NEt_3 \cdot HCO_2H$ [7] and Pd or Rh/basic support/H_2.[8]

As an alternative and analogous to the direct reductive amination,[9] the procedure can be simplified by the simultaneously addition of a reductant at the beginning of the reaction along with the substrates and optionally a base (direct reductive alkylation).[3] This convenient (non-sequential) one-pot procedure can give access to products often difficult to obtain by the aforementioned sequential process, since the condensation product can be reduced as soon as it is formed by the reductant already present in the reaction mixture.[3] For example, the one-pot reductive alkylation of Meldrum's acid with amino-boranes has been successfully applied to a number of challenging aliphatic aldehydes.[3] On the contrary, the stepwise addition of the reagents led to a predominant formation of the Michael adduct (by the reaction with a second Meldrum's acid).[3,10]

A limited number of direct reductive alkylation methods with various combinations of Knoevenagel catalysts and reductants are already known in the literature: $NaBH_4$,[11] H_2/Pd/C,[12] piperidinium acetate/H_2/rhodium,[13] proline/Hantzsch ester[1,14,15,16,17], triethylammonium formate/rhodium complex[18] and tetracarbonylhydridoferrate.[19] More recently, it has been shown that the reductive alkylation can be carried out with alcohols by using "hydrogen borrowing" strategy with homogeneous[20] or heterogeneous catalysts.[21,8a]

However, there is no general reductive alkylation method applicable to all the active methylene compounds today. In particular, dialkylmalonates remain challenging substrates.[1,12e,f,13] The direct reductive alkylation is often limited by an undesirable reduction of the starting carbonyl[11] and a Michael addition of the active methylene on the Knoevenagel adduct.[14] Furthermore in the context of green chemistry, the use of a heterogeneous catalyst and an easily separable reductant is desirable.

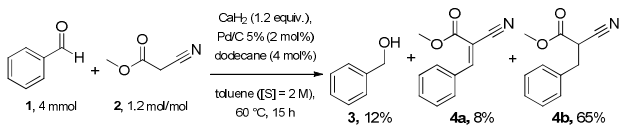
In our laboratory, we have a long standing interest in the development of new methodologies in reduction. We have been exploring the use of poorly reactive reductants in economical and eco-friendly reducing systems. Amongst alternatives, we have studied hydrosiloxanes,[22] hypophosphite derivatives[23] and calcium hydride.[24]

Calcium hydride, compared to other hydrides, has the advantage of being stable under air and inexpensive. In addition, by-products from calcium hydride are non-toxic solids and easy to separate. However, without a physical[25] or chemical activation,[26] it is unreactive as a reductant in organic chemistry.[27] We have previously developed the reductive amination of carbonyl derivatives with calcium hydride and platinum on charcoal as a catalyst.[24] We proposed that calcium hydride was activated by water during the imine formation and it generated a stoichiometric amount of hydrogen used for the following reduction. Because hydrogen is released only after the

condensation step in a stoichiometric amount, by-products from the reduction of the starting aldehyde or ketone might be avoided. Therefore, we decided to investigate the potential applicability of calcium hydride to more challenging reactions such as the reductive C-alkylation of active methylene compounds.

Reductive alkylation of methylcyanoacetate

To validate the possibility of the C-C bond formation in the presence of CaH_2, the reaction of benzaldehyde **1** and methylcyanoacetate **2** was carried out with calcium hydride (1.2 equiv.) and palladium on carbon (2 mol%) at 60 °C for 15 h in a pressure tube. Benzyl alcohol **3**, alkene **4a** and alkane **4b** were obtained in 12, 8 and 65% GC yields, respectively (Scheme 1). This preliminary result showed that calcium hydride was effective in the reductive alkylation. Presumably, calcium hydride was activated by the water formed during the condensation (Figure 1). Then, the liberated hydrogen absorbed on the Pd/C reduced the double bond. Under the reaction conditions, we noticed also the undesired reduction of benzaldehyde.



Scheme 1 Reaction of benzaldehyde and methylcyanoacetate with CaH_2 and Pd/C (GC yields were determined by the use of dodecane as an internal standard.)

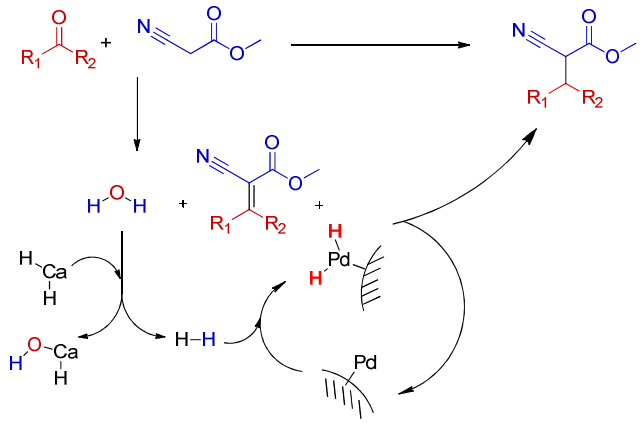


Figure 1 A proposed mechanism

This first example validated our hypothesis and drove us to conduct a deeper study to increase the efficiency of the reaction and to reduce the side product.

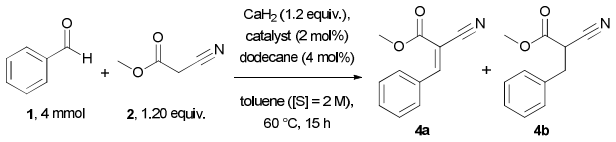
Optimisation

To improve the reduction of the intermediate alkene **4a** into alkane **4b**, the influence of heterogeneous catalysts was evaluated (Table 1). Ruthenium catalysts did not lead to the reduction of the Knoevenagel product **4a** at 60 °C (Table 1, entries 1 and 3). The temperature had to be raised to 130 °C before observing the formation of the alkane **4b** in 9% GC yield (Table 1, entry 2). In the presence of nickel catalysts, only 9-23% of benzaldehyde was converted to alkene **4a** and no subsequent reduction to the alkane **4b** was observed (Table 1, entries 4 and 5). On the contrary, the alkane **4b** was formed in 12 to 86% GC yields when palladium, platinum and rhodium catalysts were used (Table 1, entries 6-13).

However, benzyl alcohol **3** was formed as a major side product when the reaction was carried out in the presence of palladium and platinum but not in the presence of rhodium.

Palladium and platinum on silica gave better GC yields for alkane **4b**. The best results were obtained when palladium and platinum were supported on silica, giving alkane **4b** in 68 and 86% GC yields, respectively (Table 1, entries 8 and 10). Furthermore, platinum on silica did not reduce the starting benzaldehyde to benzyl alcohol, and for this reason, it was selected as the catalyst for further investigation.

Table 1 Influence of the catalyst

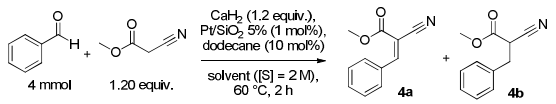


Entry	Catalyst	GC yield (%)[a]			
		1	**3**[b]	**4a**	**4b**
1	Ru/C 5% (60 °C)	0	0	95	0
2	Ru/C 5% (130 °C)	0	0	48	9
3	Ru/Al_2O_3 5%	0	0	>95	0
4	Ni SiO_2/Al_2O_3 65%	90	0	9	0
5	Ni-SiO_2 65% 5249P	75	0	23	0
6	Pd/C 5%	1	12	8	65
7	Pd/Al_2O_3 5%	8	8	51	30
8	Pd/SiO_2 5%	0	11	5	68
9	Pt/C 5%	0	15	50	12
10	Pt/SiO_2 5%	0	0	2	86
11	Pt/Al_2O_3 5%	0	7	23	45
12	Rh/C 5%	0	0	66	29
13	Rh/Al_2O_3 5%	0	0	37	54

[a] GC yields were determined by the use of dodecane as an internal standard. [b] Benzyl alcohol.

The influence of the solvent was evaluated in the presence of 1.2 mol of calcium hydride per mol of benzaldehyde (Table 2). Changing the solvent from toluene to another unpolar solvent, cyclohexane, led to a comparable GC yield of alkane **4b** (Table 2, entries 1 and 2). The reactions in THF, 2-MeTHF and CPME (cyclopentylmethyl ether) gave **4b** in 65, 53 and 13% yields, respectively (Table 2, entries 3-5). Under neat conditions, 49% of alkene **4a** remained unreduced (Table 2, entry 6). Over time, the reaction mixture got thicker and the lower yield could be explained by a difficult mass transfer slowing down the reaction. From the screening of the solvents, we observed no clear solvent effect with the exception of CPME, hence we focused our optimisation study with toluene.

Table 2 Influence of the solvent



Entry	Solvent	GC yield (%)[a]	
		4a	**4b**
1	Toluene	34	58
2	Cyclohexane	29	64
3	THF	26	65
4	2-MeTHF	46	53
5	CPME	80	13
6	Neat	49	49

[a] GC yields were determined by the use of dodecane as an internal standard.

Decreasing the catalyst loading of platinum on silica from 2 to 1 mol% led to a slight decrease in the yield of alkane **4b** from 86% to 81% (Table 3, entries 1 and 2). The reaction with silica in the absence of platinum converted 50% of benzaldehyde into alkene **4a** but no reduction took place to form **4b** (Table 3, entry 3).

When the quantity of CaH_2 was lowered from 1.2 to 0.6 equivalents, the yield of alkane **4b** increased from 81% to 87% (Table 3, entries 2 and 4). Lowering the equivalence of CaH_2 further down to 0.5 equiv. led to a 75% GC yield (Table 3, entry 5). In these conditions, almost all the hydrogen of calcium hydride must have been incorporated to the product as proposed in Figure 1.

Table 3 Influence of the catalyst loading and the amount of CaH_2[a]

Entry	Pt/SiO_2 (mol%)	CaH_2 (equiv.)	GC yield (%)[b]		
			1	**4a**	**4b**
1	2	1.2	0	2	86
2	1	1.2	0	5	81
3	0 (silica)	1.2	50	41	0
4	1	0.6	0	4	87
5	1	0.5	0	10	75

[a] Conditions: benzaldehyde (4 mmol), methylcyanoacetate (4.8 mmol, 1.2 equiv.), Pt/SiO_2 5% (mol%), CaH_2 (equiv.), toluene (2 mL), dodecane (0.16 mmol), 60 °C, rpm 700, 15 h. [b] GC yields were determined by the use of dodecane as an internal standard.

Application to different aldehydes

To exemplify the utility of the method, a range of aldehydes and ketones were subjected to the following conditions: in a pressure tube, aldehyde or ketone (4 mmol), methylcyanoacetate (1.2 equiv.), calcium hydride (0.6 equiv.), platinum on silica 5% (1 mol%) in toluene (2 M) at 60 °C for 16 hours (Table 4). In every case, an aldehyde or a ketone was completely consumed and transformed into a mixture of its corresponding alkene **a** and alkane **b**. No significant reduction of the starting aldehyde or ketone was detected. The functional group tolerance was good with no reduction of halide, nitrile and ester (Table 4, entries 2-4). The effect of the para substituent on the aldehyde appears to be important. While the electron-withdrawing groups led to nearly complete reduction of the alkenes to the alkanes, the electron-donating groups lowered the ratios of alkane/alkene (Table 4, entries 1 and 2 *versus* entries 3 and 5). A noticeable exception was the ester derivative leading to a 50/50 mixture which may be explained by the poor solubility of the starting material and the condensation product (Table 4, entry 4).

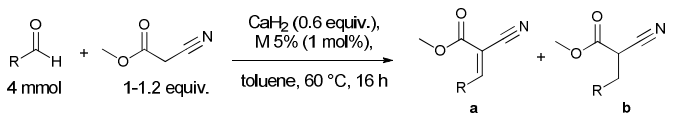
The reaction conditions are also applicable to the aliphatic aldehyde and the ketone shown in Table 4. The reductive alkylation of 3-phenylpropionaldehyde gave predominantly the alkane over the alkene in a 97/3 ratio (Table 4, entry 7). In comparison, the reaction of cyclohexanone with methylcyanoacetate led to the moderate alkane/alkene ratio of 75/25 (Table 4, entry 8).

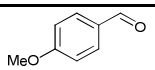
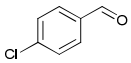
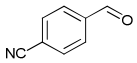
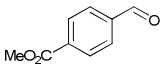
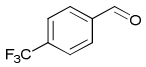
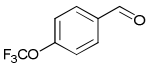
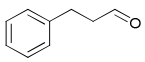
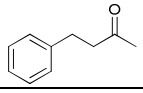
Although a good functional group tolerance was observed under these reaction conditions, the reductive alkylation catalysed by Pt on silica led in most cases to a mixture of the desired alkane and the intermediate alkene. Such a mixture is generally difficult to purify leading to a low isolated yield of the alkane. This prompted us to use palladium on charcoal as a catalyst.

When using palladium on carbon, the reaction conditions were slightly modified to a higher dilution from 2 M to 1.3 M and a strict stoichiometry between methylcyanoacetate and the carbonyl derivative. Under these conditions, the alkane/alkene ratio was improved in most cases and the alkanes were isolated in moderate to good yields (Table 4, entries 1, 3-5, 7 and 8). This improved ratio for the alkane might be attributed to the higher reduction efficiency of Pd/C compared to Pt/SiO_2. Ether, ester and nitrile were unaffected; however chloride was partially reduced under these conditions (Table 4, entries 2). The OCF_3 derivative gave a slightly lower alkane/alkane ratio of 85/15 and the alkane was isolated in 47% yield (Table 4, entry 6). The aliphatic aldehyde and the cyclic ketone were converted exclusively to their corresponding alkanes and isolated in 83 and 64% yields, respectively (Table 4, entries 7 and 8).

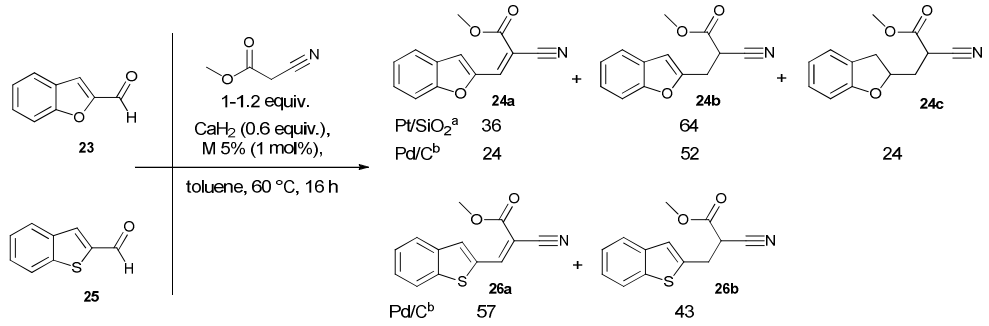
The Knoevenagel condensation of acyclic ketone **21** and methylcyanoacetate was incomplete (80% conversion), and the subsequent reductive step led to the alkane/alkene ratio of 65 to 35 (Table 4, entry 9). Separation of the alkane **22b** from its corresponding alkene was difficult, thus yielding only 5% of the isolated product. Under the reaction conditions, acetophenone gave a complex mixture of products (not shown in Table 4).

Table 4 Reductive alkylation of methylcyanoacetate with carbonyl derivatives



Entry	Aldehyde or ketone		Product number	alkane **b**/alkene **a**[a]		Isolated yield in alkane **b** with Pd/C (%)
				Pt/SiO_2[b]	Pd/C[c]	
1		**5**	**6b**	78/22	90/10[d]	54
2		**7**	**8b**	85/15	Complex mixture[e]	ND
3		**9**	**10b**	100/0	100/0	65
4		**11**	**12b**	50/50	100/0	70
5		**13**	**14b**	95/5	100/0	78
6		**15**	**16b**	-	85/15	47
7		**17**	**18b**	97/3	100/0	83
8		**19**	**20b**	75/25	100/0[f]	64
9		**21**	**22b**	-	Conversion: 80 65/35	5

[a] Alkane **b**/alkene **a** were determined by GC. [b] Aldehyde or ketone (4 mmol), methylcyanoacetate (1.2 equiv.), CaH_2 (0.6 equiv.), Pt/SiO_2 5% (1 mol%), toluene (2 M), 60 °C, 16 h. [c] Aldehyde or ketone (4 mmol), methylcyanoacetate (1 equiv.), CaH_2 (0.6 equiv.), Pd/C 5% (1 mol%), toluene (1.3 M), 60 °C, 16 h. [d] Pd/C (2 mol%), Cs_2CO_3 (10 mol%). [e] A complex mixture of dehalogenated and non-dehalogenated products was observed. [f] 100 °C, CPME instead of toluene.

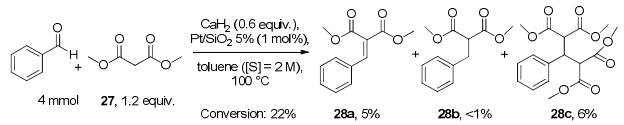


Scheme 2 Reductive alkylation of methylcyanoacetate with aldehydes bearing heterocycles (GC proportions). [a] Aldehyde or ketone (4 mmol), methylcyanoacetate (1.2 equiv.), CaH_2 (0.6 equiv.), Pt/SiO_2 5% (1 mol%), toluene (2 M), 60 °C, 16 h. [b] Aldehyde or ketone (4 mmol), methylcyanoacetate (1 equiv.), CaH_2 (0.6 equiv.), Pd/C 5% (1 mol%), toluene (1.3 M), 60 °C, 16 h.

In order to evaluate the applicability of the reductive alkylation further, heterocyclic aldehydes **23** and **25** with methylcyanoacetate were subjected to the optimised conditions with platinum and palladium (Scheme 2). In the case of 1-benzothiophene-2-carbaldehyde **25** in the presence of Pd/C, only 76% of the aldehyde was consumed and a moderate alkane/alkene ratio of 57/43 was observed. Similarly, the reductive alkylation with 1-benzofuran-2-carbaldehyde **23** in the presence of Pt/SiO_2 led to a poor alkane/alkene ratio of 36/64. When Pd/C was used as a catalyst, the benzofuran ring was reduced.

Reductive alkylation of dimethylmalonate

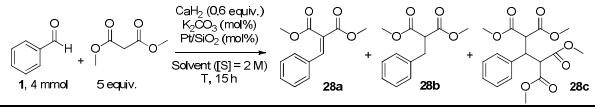
Having established the conditions for the reductive alkylation of methylcyanoacetate, we decided to tackle more challenging substrates such as dimethylmalonate. Dimethylmalonate was subjected to the reductive alkylation conditions with benzaldehyde in the presence of Pt/SiO_2 as a catalyst at 60 °C. The reaction was sluggish, and even at 100 °C only 22% of benzaldehyde was consumed (Scheme 3). In addition, a new by-product **28c** was identified, coming from the 1,4-addition of dimethylmalonate on the newly formed alkene **28a**.



Scheme 3 Reaction of benzaldehyde and dimethylmalonate with CaH_2 and Pt/SiO_2 at 100 °C (GC yields were determined by the use of dodecane as an internal standard.)

The low conversion of the aldehyde meant that the condensation step was not taking place efficiently. The reaction without a metal catalyst was carried out neat with an excess of dimethylmalonate at a higher temperature (130 °C) to favour the condensation. Surprisingly, 86% of benzaldehyde remained unreacted (Table 5, entry 1). Following the literature precedents using a carbonate as a base in a Knoevenagel condensation,[28,29] K_2CO_3 (20 mol%) was added to the reaction. The conversion of benzaldehyde was almost complete; however, the 1,4-addition product on the double bond was the major product (Table 5, entry 2). From this result, we decided to run the same reaction in the presence of Pt/SiO_2 (1 mol%) to understand the influence of potassium carbonate in the reductive alkylation. To help the stirring and to evaluate the solvent effect, a solvent was added and the temperature was lowered to 80 °C (Table 5, entries 3-6). When toluene was used, 63% of benzaldehyde was consumed and alkane **28b** and the product of diaddition **28c** were formed in 2% and 30% yields, respectively (Table 5, entry 3). Changing the solvent from toluene to THF or 2-MeTHF did not improve the yield of alkane **28b** (Table 5, entries 4 and 5). CPME, in comparison, led to an even higher yield of the diaddition product **28c** in 48% (Table 5, entry 6).

Table 5 Influence of the solvent

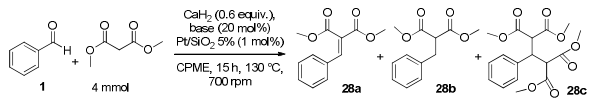


Entry	K_2CO_3 (mol%)	T (°C)	Pt/SiO_2 (mol%)	Solvent	GC yield (%)[a] 1	28a	28b	28c
1	0	130	0	none	86	1	0	6
2	20	130	0	none	11	1	0	70
3	20	80	1	toluene	37	0	2	30
4	20	80	1	THF	43	2	2	36
5	20	80	1	2-MeTHF	42	2	3	33
6	20	80	1	CPME	34	2	1	48

[a] GC yields were determined by the use of dodecane as an internal standard.

We reasoned that by reducing the proportion of malonate compared to benzaldehyde we would be able to reduce the diaddition product **28c**. The following conditions were applied: dimethylmalonate (4 mmol), benzaldehyde (1.5 equiv.), potassium carbonate (20 mol%), calcium hydride (0.6 equiv.) and Pt/SiO_2 (1 mol%) in CPME at 130 °C (Table 6, entry 1). As expected, under these conditions, the by-product **28c** from Michael addition was decreased to 10%; however, the desired alkane **28b** was formed only in 7% yield while 41% of the condensation product **28a** remained unreduced (Table 6, entry 1). The substitution of potassium carbonate by caesium carbonate improved the yield of the alkane from 7% to 46% (GC yield), but a large proportion of alkene **28a** was still observed (Table 6, entry 2).

Table 6 Optimisation studies on the reductive alkylation of dimethylmalonate



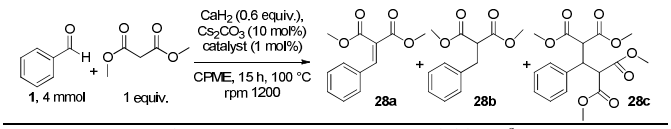
Entry	Base (mol%)	T (°C)	1 (equiv.)	GC yield (%)[a] 1	28a	28b	28c
1	K_2CO_3 (20)	130	1.5	-	41	7	10
2	Cs_2CO_3 (20)	130	1.5	-	27	46	1
3	Cs_2CO_3 (20)	130	1	7	21	44	1
4	Cs_2CO_3 (10)	130	1	9	19	42	0
5	Cs_2CO_3 (10)	100	1	6	19	47	7
6[b]	Cs_2CO_3 (10)	100	1	4	11	61	3
7[b]	Cs_2CO_3 (10)	80	1	14	15	28	19

[a] GC yields were determined by the use of dodecane as an internal standard. [b] The reaction was stirred at 1200 rpm.

The amount of benzaldehyde could be reduced from 1.5 to 1 equivalent without significant influence on the yields (Table 6, entries 2 and 3). When the amount of caesium carbonate was reduced from 20 to 10 mol% and the temperature from 130 °C to 100 °C, no significant impact on the yield of alkane **28b** was observed (Table 6, entries 3-5). Nevertheless, a lower temperature (80 °C) had a detrimental effect on the conversion and the selectivity (Table 6, entry 7). Toluene or methylcyclohexane can be used instead of CPME in the reaction while the amount of other side products was lower with CPME (not shown in Table 6). Over the parameters we screened, we found that a good stirring had a significant impact on the reaction; the yield of the saturated product **28b** was improved to 61% by increasing the stirring from 700 to 1200 rpm (Table 6, entry 6).

As it was observed in the case of methylcyanoacetate, we hoped that changing the catalyst from platinum to palladium would improve the reduction efficiency, leading to a better yield of the alkane. It turned out that palladium provided the desired product in better yields while changing the support from silica to carbon showed a slight improvement in yield (Table 7).

Table 7 Influence of the metal catalyst



Entry	Catalyst	GC yield (%)[a] 1	3[b]	28a	28b	28c
1	Pt/SiO_2 5%	4	0	11	61	3
2	Pd/SiO_2 5%	7	1	2	70	4
3	Pd/C 5%	4	2	0	79	0

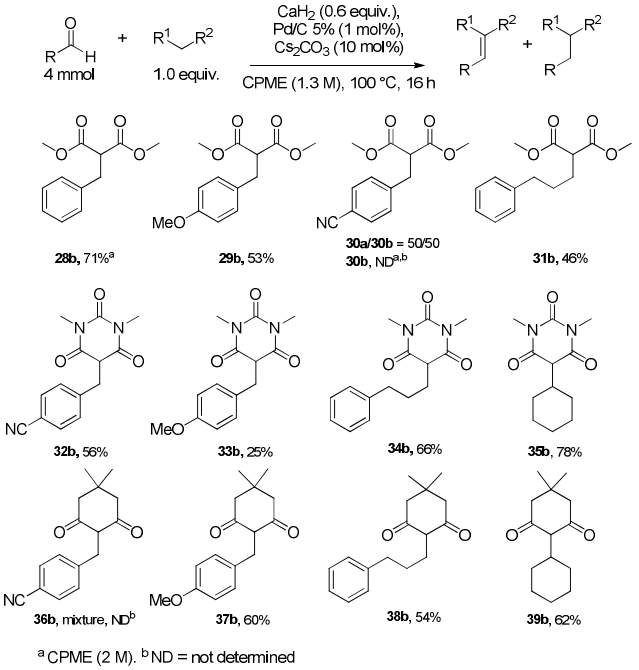
[a] GC yields were determined by the use of dodecane as an internal standard. [b] Benzyl alcohol.

After having optimised the reaction conditions, the reductive alkylation of dimethylmalonate can be successfully carried out with CaH_2 (0.6 equiv.) as a reductant in the presence of an aldehyde (1 equiv.), caesium carbonate (10 mol%) and palladium on charcoal (1 mol%) at 100 °C in CPME in a pressure tube.

Application to carbonyl derivatives

The optimised conditions were applied to a range of carbonyl derivatives to assess its applicability (Scheme 4). Amongst the benzaldehydes screened, the unsubstituted benzaldehyde and 4-

methoxybenzaldehyde led to good alkane/alkene ratios and were isolated in 71% and 53% yields, respectively. The 4-chlorobenzaldehyde **7**, on the other hand, did not condense with dimethylmalonate, and we observed mainly the dechlorination of the starting material to benzaldehyde (not shown in Scheme 4). For 4-cyanobenzaldehyde, a 50/50 mixture of alkene **30a**/alkane **30b** was observed as well as 15% of other unidentified side products. The reaction with the aliphatic aldehyde, 3-phenylpropionaldehyde **17**, led to the alkane **31b** in 46% isolated yield. The reaction with cinnamaldehyde resulted in a complex mixture, whereas the reaction with cyclohexanone led to a very low conversion of 1% as determined by GC (not shown).



[a] CPME (2 M). [b] ND = not determined

Scheme 4 Reductive alkylation of dimethylmalonate, 1,3-dimethylbarbituric acid and dimedone with different carbonyl derivatives

Application to different active methylene compounds

The reductive alkylation conditions of dimethylmalonate with calcium hydride were also applied successfully to other active methylene derivatives. Reactions with 1,3-dimethylbarbituric acid led to modest to good yields of the desired alkanes **32b-35b** in 25% to 78% (Scheme 4). Reactions with dimedone behaved differently. The reaction with *p*-cyanobenzaldehyde resulted in a mixture of products. The reaction with 4-methoxybenzaldehyde led to the expected alkane **37b** in 60% isolated yield. Aliphatic carbonyl such as 3-phenylpropionaldehyde and cyclohexanone led to the alkanes **38b** and **39b** in 54 and 62% isolated yields, respectively.

Finally the replacement of calcium hydride with molecular hydrogen under the previously optimised reaction conditions was evaluated for comparison. More precisely, the reactions of benzaldehyde with both methylcyanoacetate and dimethylmalonate were performed in an autoclave (10 bar of hydrogen pressure) under the reductive alkylation conditions described in Table 1 (with Pd/C as a catalyst) and in Scheme 4, respectively. In both cases, the analyses of the crude mixtures revealed that only benzyl alcohol was formed without a trace of the desired product. These results are in agreement with the literature data.[12f]

Conclusion

In conclusion, calcium hydride was efficiently used in the direct reductive alkylation of active methylene compounds with aldehydes and ketones, catalysed by palladium on charcoal. The reaction is applicable to methylcyanoacetate, dimedone, 1,3-dimethylbarbituric and dimethylmalonate as active methylene compounds. Concerning the carbonyl counterpart, aliphatic and aromatic aldehydes as well as cyclohexanone gave good yields, whereas, aliphatic ketones are more challenging in general.

Two sets of reaction conditions have been developed. Methylcyanoacetate reacts readily with aldehydes in the presence of calcium hydride and palladium on carbon at 60 °C. These mild conditions are also applicable to ketones although less efficiently. More challenging dimethylmalonate required the use of a carbonate base such as caesium carbonate at an elevated temperature (>100 °C). These conditions were applied successfully to other active methylene compounds such as 1,3-dimethylbarbituric acid and dimedone.

Finally, it was shown that calcium hydride is not a simple substitute to molecular hydrogen. In the presence of calcium hydride clean reductive alkylation was observed with a limited reduction of the starting aldehyde or ketone. With molecular hydrogen, this was not the case; the main product was the reduction of the starting aldehyde. We think that these results are encouraging for the further use of calcium hydride in reduction.

Experimental

General procedure A: reductive alkylation of methylcyanoacetate with Pt/SiO_2

In a sealed tube was introduced dodecane (68 mg, 0.40 mmol, 10 mol%), an aldehyde or a ketone (4.00 mmol, 1 equiv.), methylcyanoacetate (0.428 mL, 4.8 mmol, 1.2 equiv.) and toluene (2 mL, [S] = 2 M). The reaction vessel was flashed with argon, followed by the addition of Pt/SiO_2 5% (155 mg, 0.04 mmol, 1 mol%) and CaH_2 90% (110 mg, 2.35 mmol, 59 mol%). After the addition of CaH_2, the tube was sealed and introduced in a preheated oil bath at 60 °C. The reaction was stirred at 700 rpm for 15 hours. The reaction was cooled to room temperature, suspended in dichloromethane and filtered on Millipore. The filtrate was added to a 250 mL volumetric flask and diluted to 250 mL. A sample of the solution was injected in GC. From the relative area of the product and dodecane, the conversion to the monoalkylated methylcyanoacetate was calculated. Purification was carried out by flash column chromatography using a gradient of cyclohexane/ethyl acetate.

General procedure B: reductive alkylation of methylcyanoacetate with Pd/C

In a sealed tube was introduced dodecane (68 mg, 0.40 mmol, 10 mol%), an aldehyde or a ketone (4.00 mmol, 1 equiv.), methylcyanoacetate (0.396 mg, 4.0 mmol, 1.0 equiv.) and toluene (3 mL, [S] = 1.3 M). The reaction vessel was flashed with argon, followed by the addition of Pd/C 5% (85 mg, 0.04 mmol, 1 mol%) and CaH_2 90% (110 mg, 2.35 mmol, 59 mol%). After the addition of CaH_2, the tube was rapidly sealed and introduced in a

preheated oil bath at 60 °C. The reaction was stirred at 700 rpm for 15 hours. The reaction was cooled to room temperature, suspended in dichloromethane and filtered through Millipore. The analysis and purification were carried out in a similar manner than General procedure A.

General procedure C:

In a sealed tube was introduced dodecane (70.0 mg, 0.40 mmol, 10 mol%), an aldehyde or a ketone (4.00 mmol, 1 equiv.), dimethylmalonate (528 mg, 4.00 mmol, 1 equiv.) or dimedone (561 mg, 4 mmol, 1 equiv.) or 1,3-dimethylbarbituric acid (624 mg, 4.00 mmol, 1 equiv.) and CPME (3 mL, [S] = 1.3 M). The reaction was flashed with argon, followed by the addition of Pd/C 5% (85 mg, 0.04 mmol, 1 mol%), CaH_2 90% (110 mg, 2.35 mmol, 59 mol%) and Cs_2CO_3 (130 mg, 0.4 mmol, 10 mol%). After the addition of Cs_2CO_3, the tube was sealed and introduced in a preheated oil bath at 100 °C. The reaction was stirred at 1200 rpm for 15 hours. The reaction was cooled to room temperature, suspended in dichloromethane or ethyl acetate or a mixture of thereof and filtered on a pad of celite. The analysis and purification were carried out in a similar manner than General procedure A.

Acknowledgements

C.G. held a doctoral fellowship from La Région Rhône-Alpes financed to the amount of 32 116 euros. The authors are grateful for the access to the MS analysis at the Centre Commun de Spectroscopie de Masse and NMR facilities at the Université Lyon 1. E. M. deeply acknowledges the Institut de Chimie de Lyon (ICL) for financial support for scientific instrument.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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