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Highly Efficient Direct Alkylation of Activated Methylene by Cycloalkanes

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Dedicated to the memory of Professor Yoshihiro Matsumura

Keywords: C–C bond formation / Alkanes / Iron / C–H bond reactions

A simple $FeCl_2$-catalyzed C–C bond formation by direct alkylation of activated methylene by using simple cycloalkanes was developed. Several kinds of alkanes were found to react with phenyl β-ketone ester and diketone compounds to afford alkylated 1,3-dicarbonyl compounds in 10–88 % yields.

Introduction

Recently, there has been great interest in the direct transformation of C–H bonds into C–C bonds without prefunctionalizations.[1] Towards such a goal, we[2] and others[3] have developed various oxidative intermolecular C–C bond formation reactions by utilizing two different C–H bonds (Scheme 1). In these cases, the C–H bond adjacent to a heteroatom[2a–2g] or a C=C bond[2h,2i] reacts with activated methylene compounds, alkene, or alkynes to form new C–C bonds. However, it is a great challenge to use *simple alkanes (without any functional groups) to form C–C bonds by such an oxidative approach*. Traditionally, the alkylation of 1,3-dicarbonyl compounds represents one of the most common methods in organic synthesis. As an alternative, herein we wish to report *direct alkylation of 1,3-dicarbonyl compounds by using simple alkanes.*

$$\text{C–H} + \text{C–H} \xrightarrow[\text{H}_2 \text{ or H acceptor}]{\text{cat. M}} \text{C–C}$$

Scheme 1.

Results and Discussion

The pioneering work of Fenton chemistry[4] and the Gif processes[5] established the conversion of aliphatic C–H bonds into C–O bonds under mild conditions by using peroxides catalyzed by various iron catalysts.[6] We rationalized that the process may be tuned toward the formation of C–C bonds with the interception of intermediates in such reactions. To begin this study, we chose cyclohexane (**1a**) and ethyl benzoylacetate (**2a**) as the standard substrates to search for suitable reaction conditions in the presence of iron catalysts (Table 1). To our delight, desired product **3a** was obtained in 30% NMR spectroscopic yield when *tert*-butyl peroxybenzoate was used as an oxidant (Table 1, Entry 1). After numerous unsuccessful optimizations, it was found that the yield of the desired product could be increased to 52% when the reaction was performed under an atmosphere of nitrogen (Table 1, Entry 3). Then, various oxidants were tested under such conditions and all led to the desired product with various efficiencies. The only exception was *tert*-butyl hydroperoxide (TBHP) with which no reaction was observed (Table 1, Entries 2–8). The desired product could be obtained in 79% yield when *tert*-butyl peroxide was used as the oxidant (Table 1, Entry 8). On the basis of this result, various iron catalysts were examined: $FeCl_2$, $FeBr_2$, $FeCl_3$, and $FeCl_3{\cdot}6H_2O$ also gave good yields for this reaction (Table 1, Entries 9–13). No desired product was detected by ^1H NMR spectroscopic analysis when $Fe(NO)_3{\cdot}9H_2O$, $FeSO_4{\cdot}XH_2O$, $Fe(C_2O_4){\cdot}2H_2O$, $Fe(acac)_3$, or other metal salts such as $CuCl{\cdot}5H_2O$, $Cu(OAc)_2$, $CuSO_4{\cdot}5H_2O$, or $CuCl_2$ were used as the catalysts (Table 1, Entries 14–17). Albeit still effective, lowering the reaction temperature significantly decreased the rate of the reaction (Table 1, Entry 18). A reduction in the amount of either the catalyst or *tert*-butyl peroxide resulted in a marked decrease in the product yield (Table 1, Entries 19 and 20). Interestingly, in the absence of any iron catalyst, a trace amount of coupling product **3a** was still generated (Table 1, Entry 23).

Subsequently, under the optimized reaction conditions, various activated methylene substrates were treated with cy-

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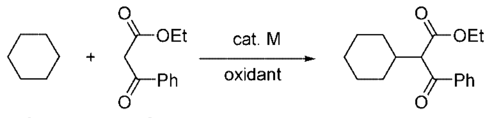
Table 1. Optimization of reaction conditions.[a]



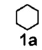
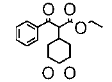
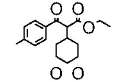
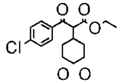
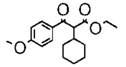
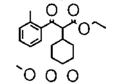
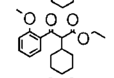
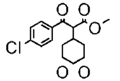
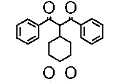
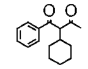
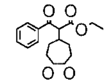
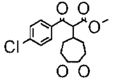
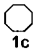
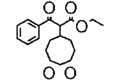
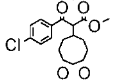
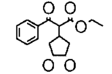
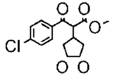
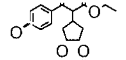
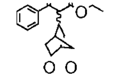
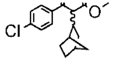
1a + **2a** → **3a**

Entry	Catalyst (mol-%)	Oxidant (equiv.)	T [°C]	Yield [%][b]
1[c]	$FeCl_2·4H_2O$ (20)	PhC(O)OO*t*Bu (2.0)	100	30
2	$FeCl_2·4H_2O$ (20)	TBHP (2.0)	100	N.D.[d]
3	$FeCl_2·4H_2O$ (20)	PhC(O)OO*t*Bu (2.0)	100	52
4	$FeCl_2·4H_2O$ (20)	Di(*tert*-butylperoxyisopropyl)benzene (1.0)	100	60
5	$FeCl_2·4H_2O$ (20)	$PhC(CH_3)_2OOC(CH_3)_2Ph$ (2.0)	100	75
6	$FeCl_2·4H_2O$ (20)	$PhC(CH_3)_2OOtBu$ (2.0)	100	75
7	$FeCl_2·4H_2O$ (20)	PhC(O)OOC(O)Ph (2.0)	100	35
8	$FeCl_2·4H_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	79
9	FeF_2 (20)	*t*BuOO*t*Bu (2.0)	100	<5
10	$FeCl_2$ (20)	*t*BuOO*t*Bu (2.0)	100	75
11	$FeBr_2$ (20)	*t*BuOO*t*Bu (2.0)	100	65
12	$FeCl_3$ (20)	*t*BuOO*t*Bu (2.0)	100	65
13	$FeCl_3·6H_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	70
14	$Fe(NO_3)_3·9H_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	N.D.[d]
15	$FeSO_4·XH_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	N.D.[d]
16	$Fe(C_2O_4)·2H_2O$ (20)	*t*BuOO*t*Bu (2.0)	100	N.D.[d]
17	$Fe(acac)_3$ (20)	*t*BuOO*t*Bu (2.0)	100	N.D.[d]
18	$FeCl_2·4H_2O$ (20)	*t*BuOO*t*Bu (2.0)	75	40
19	$FeCl_2·4H_2O$ (10)	*t*BuOO*t*Bu (2.0)	100	20
20	$FeCl_2·4H_2O$ (20)	*t*BuOO*t*Bu (1.0)	100	54
21	$FeCl_2·4H_2O$ (40)	*t*BuOO*t*Bu (2.0)	100	80
22	$FeCl_2·4H_2O$ (20)	*t*BuOO*t*Bu (4.0)	100	75
23	--------------	*t*BuOO*t*Bu (2.0)	100	<5

[a] Ethyl benzoylacetate (0.2 mmol), cyclohexane (4.0 mmol), 12 h under N_2; unless otherwise noted; TBHP (5–6 M in decane). [b] NMR spectroscopic yields by using an internal standard. [c] Ethyl benzoylacetate (0.2 mmol), cyclohexane (1.0 mL), 12 h. [d] Not detected by NMR spectroscopy.

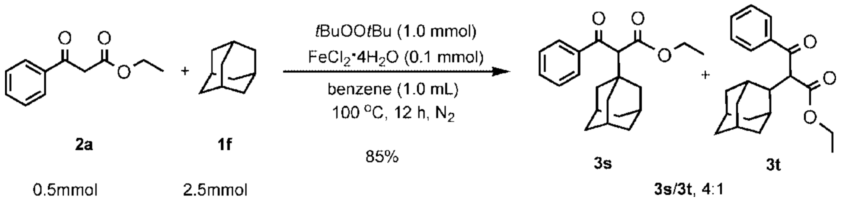
clohexane, cyclopentane, cycloheptane, cyclooctane, norbornane, or adamantane. The representative results are summarized in Table 2. With cyclohexane, various aryl β-keto esters provided the desired alkylation products, mostly in good yields (Table 2, Entries 1–7). The use of diketones led to lower conversions relative to those obtained with the use of β-keto esters (Table 2, Entries 8 and 9). When a cyclic diketone was used, a complicated mixture was obtained owing to the self-reaction of the cyclic diketone. In contrast, various cyclic alkanes (five-, seven-, or eight-membered rings) were transformed into the desired products in good yields when treated with the β-keto esters (Table 2, Entries 10–16). Reaction of norbornane with **2a** (and **2g**) gave the alkylation products as a mixture of two diastereoisomers in a 1:1 ratio (Table 2, Entries 17 and 18). On the basis of the ^1H NMR spectrum of the crude reaction mixture, no product resulting from the reaction of the bridgehead C–H bond was detected. Quite the reverse was found when adamantane was treated with ethyl benzoylacetate (**2a**): a 4:1 mixture of the alkylation products was obtained with the major isomer corresponding to the coupling at the more-substituted carbon atom (Scheme 2). It is worth mentioning that simple *n*-hexane is also effective in this reaction. Its alkylation with β-keto ester **2a** gave two regioisomers corresponding to the reaction of the two types of methylene C–H bonds in *n*-hexane. The slightly higher ratio of the product corresponding to alkylation at the C3 methylene rather than the one at the C2 methylene could be attributed to the more stable radical at the C3 position. No product was isolated due to the reaction of the C–H bonds at the terminal methyl groups (Scheme 3).

Table 2. $FeCl_2$-catalyzed alkylation of alkane C–H bonds.[a]

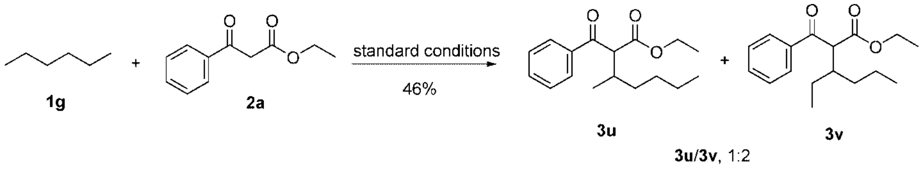
Entry	Alkane	Products		Yield [%][b]
1	 **1a**		**3a**	88
2	**1a**		**3b**	74
3	**1a**		**3c**	64
4	**1a**		**3d**	75
5	**1a**		**3e**	48
6	**1a**		**3f**	83
7	**1a**		**3g**	84
8	**1a**		**3h**	15
9	**1a**		**3i**	10
10	 **1b**		**3j**	75
11	**1b**		**3k**	70
12	 **1c**		**3l**	77
13	**1c**		**3m**	76
14[c]	 **1d**		**3n**	38
15	**1d**		**3o**	82
16	**1d**		**3p**	72
17	 **1e**		**3q**	82 (1:1)
18	**1e**		**3r**	49 (1:1)

[a] Conditions: **1** (10 mmol), **2** (0.5 mmol), *tert*-butyl peroxide (1.0 mmol), $FeCl_2·4H_2O$ (0.1 mmol), 100 °C, 12 h, N_2. [b] Isolated yields are reported; the ratios of two isomers are reported in the parentheses. [c] 23 % of **2a** remained after reaction.

A tentative mechanism for this novel C–C bond formation process by the reaction of simple alkane C–H bonds is proposed in Scheme 4. Iron(II) could catalyze the decomposition of the peroxide to give RO· and an RO-Fe(III) species.

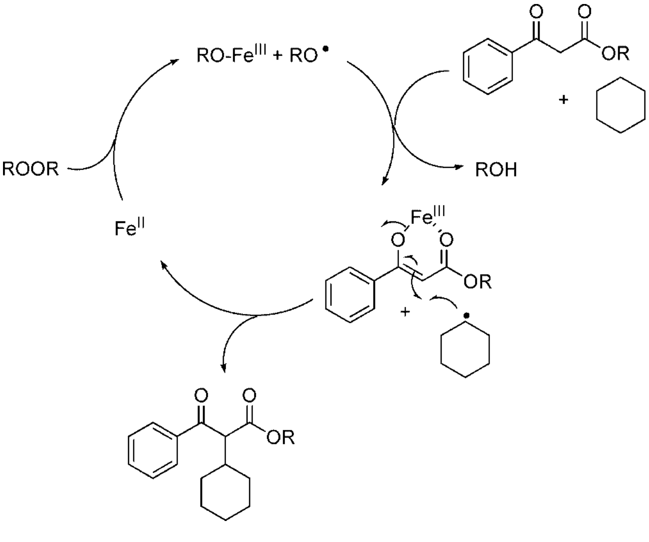


Scheme 2. Alkylation of ethyl benzoylacetate with adamantane.



Scheme 3. Alkylation of ethyl benzoylacetate by *n*-hexane.

The RO$^{\cdot}$ radical species could then react with cyclohexane to give a cyclohexyl radical, whereas RO–Fe(III) could react with the β-keto ester to generate an Fe enolate. The cyclohexyl radical is able to react with the enolate to form the alkylated β-keto ester to regenerate Fe^{II} for further reactions. Alternatively, the reaction could be considered as a simple free-radical addition onto a double bond[7] of an iron benzoylacetate; albeit no product was observed with other metal salts.



Scheme 4. Tentative mechanism for the Fe-catalyzed alkylation with simple alkanes.

Conclusion

In summary, we developed a novel method for C–C bond formation by a FeCl$_2$-catalyzed alkane C–H oxidative activation. This study provides a stepping stone for further research on the efficient functionalization of simple alkanes for chemical syntheses and energy applications. Further investigations including the mechanism, the scope, and synthetic applications of this reaction are in progress.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for all compounds.

Acknowledgments

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