Thiourea-catalyzed Oxidative Coupling Reaction of N-Phenyl Tetrahydroisoquinoline with β-Keto Acids

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The direct transformation of C-H into C-C bonds has recently received considerable attention from synthetic organic chemists.¹ Among these reactions, the direct oxidative cross-dehydrogenative coupling (CDC) of two C-H bonds can be an atom- and step-economic strategy in synthetic organic chemistry.² Since the pioneering work on CDC demonstrated by the Murahashi and Li groups on formation of oxidative iminium ions from tetrahydroisoquinoline (THIQ) derivatives,³ various nucleophiles have been utilized to combine the iminium ions to construct new C-C bonds under Mannich-type protocols.⁴ Recently, several groups have reported phenacylmethylation to form C1-phenacylmethylated THIO derivatives from the reaction of enol silanes or acetophenones using transition metals as catalysts, visiblelight mediated photocatalysis, mechanochemical process, or organic oxidants.⁵ Very recently, Zhang and coworkers reported the efficient thiourea-catalytic CDC of C(sp³)-H with phosphites and nitroalkanes by using peroxide as a terminal oxidant.⁶ The decarboxylative additions of β -keto acids as ketones or ketone enolate equivalents have received much attention.⁷ We envisioned the decarboxylative Mannich-type reaction of the β -keto acids to the C1-acylmethylated THIQs by organocatalytic CDC under mild conditions.

As part of a research program related to redox reaction, we recently reported the internal redox reaction via C-H bond activation.^{5f,8} Herein, we report the C1phenacylmethylation of THIQs with \beta-keto acids using thiourea organocatalyst. To determine the optimal reaction conditions for the thiourea-catalyzed oxidative coupling reaction of THIQs, we examined the organocatalytic reaction of N-phenyl tetrahydroisoquinoline (1) with 3-oxo-3phenylpropanoic acid (2a) in the presence of tert-butyl



Figure 1. Structures of organocatalysts.

hydroperoxide (TBHP) with 20 mol% of organocatalysts (Figure 1). By screening catalysts (Table 1, entries 1-5), we found that thiourea catalyst IV was a suitable catalyst for oxidative coupling reaction, affording the corresponding product 3a in an 84% yield (Table 1, entry 4). Among the solvents evaluated (Table 1, entries 4 and 7-13), the best result was achieved when the reaction was conducted in acetonitrile (Table 1, entry 4). The control experiment showed that the reaction could not proceed in the absence of thiourea catalyst IV (Table 1, entry 14). A trace amount of product 3a was detected in the presence of the radical inhibitor (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl

Table 1. Optimization of the reaction conditions.^a



Entry	Catalyst	Solvent	Time (h)	Yield $(\%)^b$
1	l	CH ₃ CN	20	74
2	II	CH ₃ CN	20	29
3	Ш	CH ₃ CN	20	58
4	IV	CH ₃ CN	20	84
5	V	CH ₃ CN	48	23
6	VI	CH ₃ CN	48	25
7	IV	CH_2Cl_2	20	48
8	IV	CHCl ₃	20	40
9	IV	EtOAc	24	33
10	IV	THF	20	20
11	IV	EtOH	20	21
12	IV	DMF	24	34
13	IV	PhMe	24	45
14^c		CH ₃ CN	20	Trace
15 ^d	IV	CH ₃ CN	24	Trace

^{*a*} Reaction conditions: *N*-phenyl tetrahydroisoquinoline (1, 0.3 mmol), 3-oxo-3-phenylpropanoic acid (2a, 0.45 mmol), TBHP (0.6 mmol), catalyst (0.06 mmol), solvent (2.0 mL) at room temperature. ^b Isolated yield.

^c Reaction was carried out without a catalyst.

^d Reaction was carried out in the presence of 2.0 equiv of TEMPO.

Table 2. Substrate scope.^a



Entry	2 , R	Time (h)	Yield $(\%)^b$
1	Ph	20	3a , 84
2	$4\text{-}\text{F},\text{C}_6\text{H}_4$	20	3b , 82
3	$4-Cl,C_6H_4$	24	3c , 78
4	$4\text{-Br,C}_6\text{H}_4$	24	3d , 81
5	$3-Br,C_6H_4$	24	3e , 77
6	$4-NO_2, C_6H_4$	15	3f , 75
7	4-OMe,C ₆ H ₄	12	3 g, 88
8	4-Me,C ₆ H ₄	10	3h , 76
9	3-Me,C ₆ H ₄	20	3i , 73
10	2-Me,C ₆ H ₄	48	3j , 73
11	1-Naphthyl	36	3k , 82
12	2-Furyl	36	31 , 79
13	2-Thienyl	36	3m , 74
14	CH ₃ CH ₂	48	3n , 61

^a Reaction conditions: *N*-phenyl tetrahydroisoquinoline (1, 0.3 mmol),
3-oxoalkanoic acid 2 (0.45 mmol), TBHP (0.6 mmol), catalyst (IV,

0.06 mmol), acetonitrile (2.0 mL) at room temperature.

^b Isolated yield.

(TEMPO) (Table 1, entry 15). The inhibitory effect of TEMPO indicated that this reaction proceeded via radical intermediate(s).

After determining the optimal reaction conditions, we investigated the scope of this thiourea-catalyzed oxidative coupling reaction of *N*-phenyl tetrahydroisoquinoline (1) with 3-oxoalkanoic acid **2** in the presence of 20 mol% of thiourea catalyst **IV** in acetonitrile at room temperature. As shown in Table 2, various 3-oxoalkanoic acids **2** with electron-donating or electron-withdrawing substituents in aryl groups afforded the corresponding coupling products with moderate to high yields (73–88%, Table 2, entries 1–10). The naphthyl- and heteroaryl-substituted β -keto acids provided the desired products with high yields (74–82%, Table 2, entries 11–13). In addition, alkyl-substituted β -keto acid, 3-oxopentanoic acid, also afforded the corresponding product **3n**, but with relatively lower yield (61%, Table 2, entry 14).

In conclusion, we presented a novel and environmentally benign process for the thiourea-catalyzed oxidative coupling reaction of N-phenyl tetrahydroisoquinoline (1) with 3-oxoalkanoic acid acids 2 in the presence of thiourea catalyst IV.

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