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Oxidative coupling of formamides with β-dicarbonyl compounds and the synthesis of 2-aminobenzothiazole using Cu(II)-functionalized Fe_3O_4 nanoparticles

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This article is dedicated to memory of Mostafa Chamran.

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ABSTRACT

The Fe_3O_4@EDTA–Cu(II) nanoparticles catalyzed oxidative coupling of formamides with β-dicarbonyl compounds is developed using *tert*-butyl hydroperoxide as an oxidant. In general, the enol carbamates are synthesized in excellent yields (up to 92%) under the optimized reaction conditions. Fe_3O_4@EDTA–Cu(II) has the advantage of being magnetically recoverable. Also, we have established a highly efficient Fe_3O_4@EDTA–Cu(II)-catalyzed tandem reaction of 2-iodoanilines with isothiocyanates for the synthesis of 2-aminobenzothiazoles.

Direct C–H functionalization for the formation of C–C and C–X (X = O, S, N, P, etc.) bonds catalyzed by transition metals has become a very useful tool in organic chemistry owing to its remarkable potential for step economy, atom economy, and environmental sustainability.[1] Oxidative C(sp)–H and C(sp^2)–H cross-couplings for various C–C bond-forming reactions have received significant attention and excellent progress has been made.[2] The direct C–H activation path has made the synthesis of functionalized molecules more efficient by minimizing the number of synthetic steps. Cross-dehydrogenative coupling protocols have been employed to access a diverse range of C–X bonds (X = C, heteroatom), by functionalizing C–H bonds of all types (sp, sp^2, sp^3).[3] Copper mediates different reaction types due to the ability of the copper atom to act as a Lewis acid, a single-electron mediator, and a two-electron mediator. Also, Cu-X species generated as reaction intermediates can act as either a nucleophile or an electrophile, depending on the reaction conditions and oxidation state of the copper atom. These properties of copper species account for the high utility of copper catalysts in C–X (X = C, N, O, etc.) bond formation.[4] Oxidative coupling combines two molecular entities through an oxidative process, usually catalyzed by a transition metal compound and involving dioxygen as the oxidant.[5]

In vivo data support the pharmacological efficacy of enol carbamates as promising anxiolytic therapeutics.[6] Carbamates are mixed ester–amides of carbonic acid. Their chemical behavior is similar to that of carbonates. Dixneuf et al. have shown that enol carbamates can be prepared by addition of carbamic acids to terminal alkynes catalyzed by $Ru_3(CO)_{12}$[7] or $Ru(Cl)_3$,[8] where the yields and selectivities of the carbamates are low for aliphatic acetylenes. Also, Watanabe et al. have reported that a bis(η5-cyclooctadienyl)ruthenium or Ru(COD)(CCT)-tertiary phosphine system catalyzes the reaction of secondary amines with carbon dioxide and terminal alkynes to give enol carbamates in good yields.[9] Oxidative C–O coupling by direct C–H bond activation of formamides has been accomplished in the presence of $CuBr_2$, but the main problem of this reaction is that it suffers from the loss of the catalyst at the end of the reaction.[10] Therefore, the development of EDTA@Cu(II) functionalized superparamagnetic nanoparticle-catalyzed C–O cross-coupling methods would be of value. Herein, we report a Cu-catalyzed dehydrogenative cross-coupling reaction for C–O bond formation to construct enol carbamates using *tert*-butyl hydroperoxide (TBHP) as the oxidant. We have previously reported the preparation of EDTA@Cu(II) functionalized superparamagnetic nanoparticles,[11] and their application as a highly efficient and

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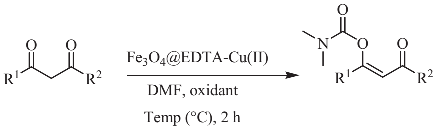


Scheme 1. Oxidative coupling of *N*,*N*-dimethylformamide with β-dicarbonyl compounds in the presence of Fe_3O_4@EDTA–Cu(II).[16]

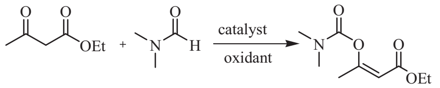
magnetically separable catalyst for the direct oxidative amidation of benzyl alcohols.[12] In continuation of our interest in using magnetic nanoparticles as a catalyst support,[13] herein, we demonstrate the oxidative coupling of formamides with β-dicarbonyl compounds in the presence of Fe_3O_4@EDTA@Cu(II) with TBHP. Various enol carbamates were obtained in good to excellent yields in a one-pot manner under our conditions (Scheme 1). Since benzothiazole is a common building block in biological compounds[14] and functional molecules,[15] we were encouraged to synthesize *N*-substituted-2-aminobenzothiazoles from 2-iodobenzenamine and isothiocyanates. 2-Aminobenzothiazoles were generated in excellent yields under mild reaction conditions in an aqueous medium. Moreover, the catalyst was recovered quantitatively from the reaction mixture with an external magnet and reused for five cycles with almost consistent activity.

Thus, we describe the development of a cheap and convenient copper catalyst system for the oxidative coupling of formamides with β-dicarbonyl compounds with TBHP as an external oxidant to give enol carbamates (Scheme 1).

The investigation began by attempting the oxidative coupling of ethyl acetoacetate using the Fe_3O_4@EDTA–Cu(II) catalyst in the presence of various oxidants. When TBHP was used as an external oxidant and *N*,*N*-dimethylformamide (DMF) as the substrate and solvent, we found that Fe_3O_4@EDTA–Cu(II) could promote coupling of ethyl acetoacetate with DMF to afford the corresponding enol carbamate (Table 1, entry 4). The amount of catalyst was initially optimized: it was found that 20 mg of Fe_3O_4@EDTA–Cu(II) was sufficient to promote the reaction (entry 6). The effects of different temperatures were also evaluated. Increasing the temperature is generally effective for the oxidative coupling of ethyl acetoacetate with DMF. As can be seen from (Table 1), 80 °C proved to be the most suitable reaction temperature (entry 9), and increasing the temperature to 100 °C did not enhance the yield of the corresponding enol carbamate further (entry 10). The reaction was then carried out in the absence of the catalyst and the oxidant, separately, which did not result in the formation of the product (entries 11 and 12).

Having established optimum conditions, we next examined the range of β-dicarbonyl compounds to which this oxidation coupling could be applied **(1a–1l)**, and the results are summarized in (Table 2).[17]

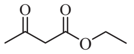
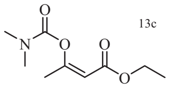
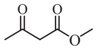
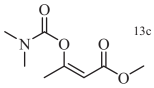
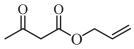
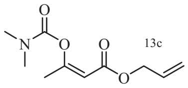
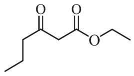
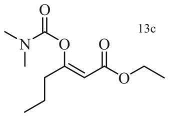
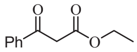
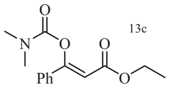
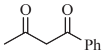
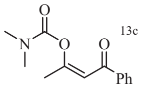
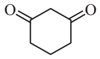
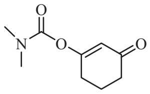
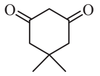
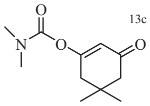
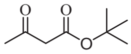
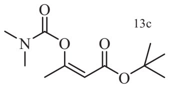
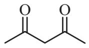
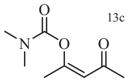
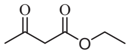
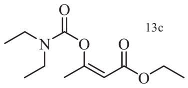
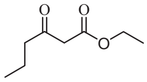
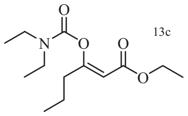
Table 1
Results of screening the conditions[a]



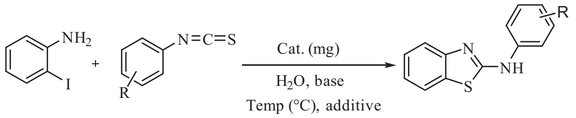
Entry	Oxidant	Catalyst (mg)	Temp (°C)	Yield[b] (%)
1	H_2O_2	5	rt	<10
2	*m*CPBA	5	rt	<10
3	UHP[c]	5	rt	<5
4	TBHP	5	rt	30
5	TBHP	10	rt	51
6	TBHP	20	rt	62
7	TBHP	20	40	73
8	TBHP	20	60	84
9	**TBHP**	**20**	**80**	**90**
10	TBHP	20	100	90
11	TBHP	—	80	—
12	—	20	80	—

[a] All reactions were run with ethyl acetoacetate (1 mmol), DMF (2 mL), oxidant (1.5 equiv), 2 h.
[b] Isolated yield.
[c] UHP = urea hydrogen peroxide.

Table 2
Synthesis of enol carbamate derivatives[a]

Entry	Substrate	Product[Ref]		Yield[b] (%)
1		 13c	**1a**	90
2		 13c	**1b**	92
3		 13c	**1c**	87
4		 13c	**1d**	85
5		 13c	**1e**	84
6		 13c	**1f**	88
7			**1g**	82
8		 13c	**1h**	80
9		 13c	**1i**	88
10		 13c	**1j**	82
11		 13c	**1k**	90
12		 13c	**1l**	86

[a] Reaction conditions for the synthesis of enol carbamates: 1,3-dicarbonyl compound (1 mmol), *N*,*N*-dialkyl formamide (2 mL), TBHP (1.5 equiv), cat. (20 mg), 80 °C, 2 h.
[b] Isolated yields.



Scheme 2. Synthesis of 2-arylaminobenzothiazoles in the presence of Fe_3O_4@-EDTA–Cu(II).[18]

Table 3
Results of screening the conditions[a]

Entry	Base	Catalyst (mg)	Temp (°C)	Additive	Yield[b] (%)
1	NaOH	5	rt	–	<10
2	KOH	5	rt	–	<10
3	K_2CO_3	5	rt	–	30
4	Na_2CO_3	5	rt	–	35
5	$NaHCO_3$	5	rt	–	15
6	Et_3N	5	rt	–	20
7	DABCO	5	rt	–	42
8	DABCO	10	rt	–	50
9	DABCO	20	rt	–	58
10	DABCO	30	rt	–	57
11	DABCO	20	40	–	65
12	DABCO	20	50	–	70
13	DABCO	20	60	–	70
14	DABCO	20	50	SDS[c]	80
15	DABCO	20	50	TBAF	75
16	**DABCO**	**20**	**50**	**TBAB**	**94**
17	DABCO	–	50	TBAB	<10
18	–	20	50	TBAB	<10
19	DABCO	20[d]	50	TBAB	–
20	DABCO	20[e]	50	TBAB	–

[a] All reactions were run with 2-iodoaniline (1 mmol), phenyl isothiocyanate (1.1 mmol), H_2O (2.0 mL), base (2 mmol), additive (10 mol %), 3 h.

[b] Isolated yield.

[c] Sodium dodecyl sulfate.

[d] In the presence of Fe_3O_4.

[e] In the presence of Fe_3O_4@EDTA.

Following the successful C–O coupling of *N*,*N*-dialkyl formamides with 1,3-dicarbonyl compounds, the reaction between 2-iodoaniline and phenyl isothiocyanate was found to be facilitated leading to the desired product in high yields (Scheme 2). The effects of the base, solvent, temperature, and reaction time were investigated, and the results are summarized in Table 3. In the absence of a base the reaction failed to generate the desired product and only 1-(2-iodophenyl)-3-phenylthiourea, as an intermediate, was obtained, even after heating for 10 h. In the presence of strong inorganic bases such as KOH and NaOH, only a small amount of the corresponding product was formed (Table 3, entries 1 and 2). The desired product **2a** was obtained in moderate yields using weak bases (K_2CO_3 or Na_2CO_3) (entries 3 and 4). Further screening revealed that DABCO was the most efficient base and the yield was somewhat improved (entry 7). Other bases such as $NaHCO_3$ and Et_3N were evaluated, however, lower yields were obtained (entries 5 and 6). Increasing the amount of catalyst from 10 to 20 mg resulted in an increase of the yield (entry 9). Next, the effect of the temperature was investigated. The yield increased to 70% from 65% when the temperature was increased to 50 °C from 40 °C (entries 11 and 12). Raising the reaction temperature further did not improve the yield (entry 13). Interestingly, the use of tetrabutylammonium bromide (TBAB) (1 mol %), led to the complete disappearance of the starting materials after three hours and the product was isolated in a high yield (94%) (entry 16). TBAB as a promoter in organic reactions can lead to higher yields and eliminates the need for dangerous organic solvents. The reaction in the presence of Fe_3O_4 and Fe_3O_4@EDTA without Cu was investigated and the results proved that Cu was essential for the reaction to occur (entries 19 and 20).

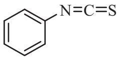
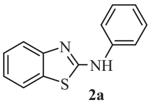
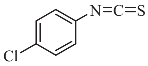
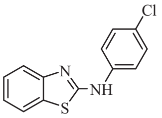
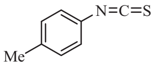
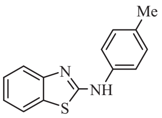
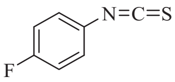
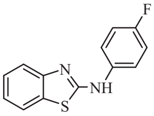
Thus, the optimal reaction conditions were 20 mg of catalyst in the presence of two equivalents of DABCO in water for two hours at 50 °C.

Under these conditions, various isothiocyanates were used as substrates for the formation of the corresponding 2-arylaminobenzothiazoles **(2a–2d)** (Table 4).[19]

The proposed mechanism for this coupling of *N*,*N*-dimethylformamide with β-dicarbonyl compounds in the presence of Fe_3O_4@EDTA–Cu(II) is shown in Scheme 3. The copper complex generated from a copper salt with β-dicarbonyl compounds may coordinate with DMF and undergo an internal nucleophilic addition to form copper hemiacetal species **1**. The intermediate **3** may abstract a hydrogen atom which leads to compound **5**. The radical generated from the copper-catalyzed decomposition of TBHP followed by a single-electron transfer (SET) in the hemiacetal radical **6** gives the desired ester.

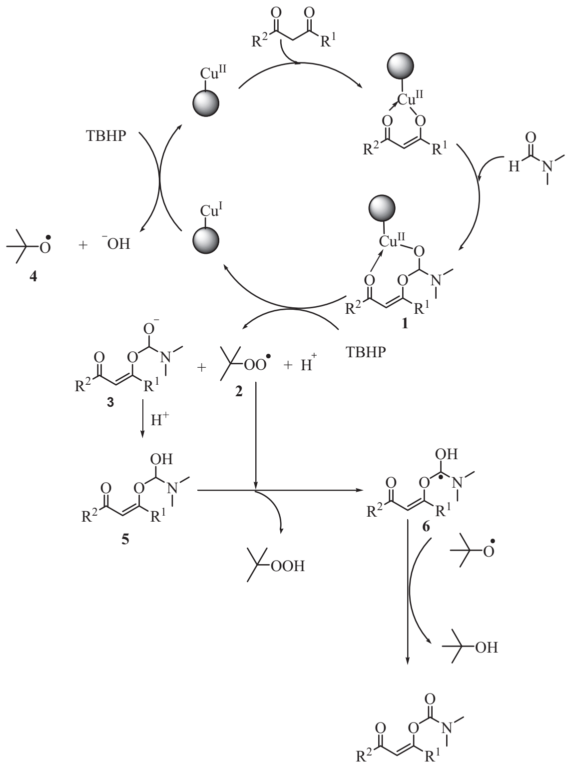
A plausible mechanism for the formation of 2-arylaminobenzothiazoles from 2-iodoanilines and isothiocyanates is shown in Scheme 4. The nucleophilic nitrogen atom of 2-iodoaniline can attack the NCS carbon atom to form an intermediate in the presence of DABCO as the base. The copper is then coordinated to the

Table 4
Fe_3O_4@EDTA–Cu(II)-catalyzed reactions of 2-iodoaniline with isothiocyanates[a]

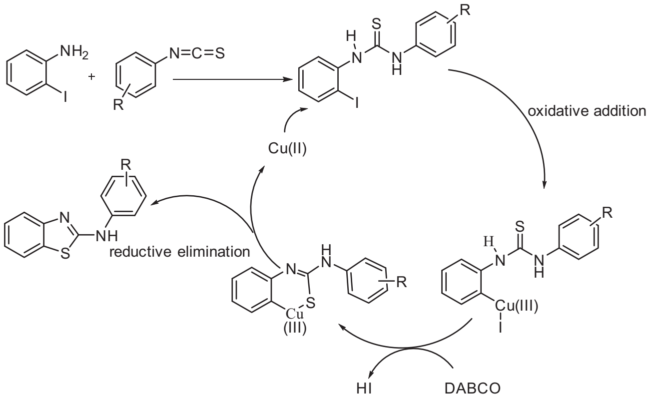
Entry	Substrate	Product	Mp (°C) (Lit.)	Yield[b] (%)
1		 **2a**	158–160 (158–160)[20]	91
2		 **2b**	210 (208–209)[20]	75
3		 **2c**	177–179 (178–179)[20]	85
4		 **2d**	219–220 (216–217)[20]	87

[a] Reaction conditions: 2-iodoaniline (1 mmol), isothiocyanate (1.1 mmol), Fe_3O_4@EDTA–Cu(II) (20 mg), DABCO (2 mmol), H_2O (2.0 mL), TBAB (10 mol %), 50 °C, 3 h.

[b] Isolated yields.



Scheme 3. Proposed mechanism for the coupling of *N*,*N*-dimethylformamide with β-dicarbonyl compounds in the presence of Fe_3O_4@EDTA–Cu(II).



Scheme 4. Proposed mechanism for the formation of 2-arylaminobenzothiazoles in the presence of Fe_3O_4@EDTA–Cu(II).

intermediate. Finally, reductive elimination produces the desired product with regeneration of the catalyst.

The reusability of Fe_3O_4@EDTA–Cu(II), in the synthesis of compound **2a** was studied. After each reaction, the catalyst was easily separated out using an external magnet, washed with ethyl acetate, and sonicated in dichloromethane for 10 min to remove any organic impurities. It was then dried at 80 °C and reused for the next cycle, without further activation. As exemplified in Figure 1, the catalyst could be reused for five consecutive reactions.

To rule out any contribution of homogeneous catalysis, we tested for leaching. After 10 min from the beginning of the reaction and removal of the catalyst using a magnet, no further formation of any product was observed, even after 24 h. This clearly confirmed that the active species did not leach into the solvent.

In conclusion, several features of this robust system are worth noting: the catalytic system is able to be applied effectively to a wide range of β-dicarbonyl compounds for the synthesis of enol carbamates and Fe_3O_4@EDTA–Cu(II) can be used for at least five consecutive runs without any significant loss of its catalytic activity. Also, this catalyst provides an efficient, and practical route for the generation of 2-arylaminobenzothiazoles. It has the advantage of being magnetically recoverable, therefore removing the requirement for catalyst filtration after the reaction.

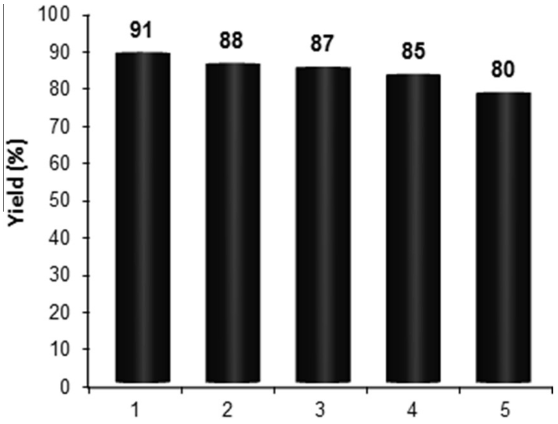


Figure 1. Recyclability of the Fe_3O_4@EDTA–Cu(II) catalyst for the synthesis of **2a** (reaction time: 3 h).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.110.

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11. *The surface modification of Fe_3O_4:* The magnetic catalyst [Fe_3O_4@EDTA–Cu(II)] was prepared by dissolving a mixture of $FeCl_3 \cdot 6H_2O$ (10 mmol) and $FeCl_2 \cdot 4H_2O$ (5 mmol) salts in deionized H_2O (100 mL) under vigorous stirring (800 rpm). NH_3 (aq) solution (25%, w/w, 30 mL) was then added dropwise to the stirred mixture to maintain the reaction pH at about 11. Next, EDTA (disodium salt dihydrate) solution (1.1 g, 2 mmol in 20 mL water) was added to the black suspension. The resulting black dispersion was stirred for 1 h at room temperature and was then refluxed for 1 h. Fe_3O_4 nanoparticles were separated from the aqueous solution by decantation and applying a magnet, and washed with H_2O several times. Subsequently, $CuCl_2 \cdot 2H_2O$ (2 mmol) in H_2O (50 mL) and Na_2CO_3 (4 mmol) were added and the mixture was stirred at 40 °C for 6 h. The suspension was refluxed for 2 h. Finally, the nanoparticles were separated from the aqueous solution by decantation and applying a magnet, and then washed with H_2O, EtOH and Et_2O several times before being dried in an oven overnight.

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16. *Oxidative coupling of DMF with 1,3-cyclohexanedione:* To a mixture of Fe_3O_4@EDTA–Cu(II) (20 mg), DMF (2 mL), and 1,3-cyclohexanedione (1 mmol) was added *tert*-butyl hydroperoxide (TBHP) (1.5 equiv, 0.193 g, 70 wt % in H_2O) under an inert atmosphere (N_2). The reaction vessel was capped and the contents stirred for 2 h at 80 °C. After cooling to rt, the catalyst was removed using an external magnet. The combined organics were extracted with EtOAc (2 × 10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude residue, which was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to provide the desired product **1g** as clear yellow oil.
17. *3-Oxocyclohex-1-enyl dimethyl carbamate* (**1g**): Yellow oil, isolated yield = 82%; IR cm^{-1}: IR (KBr, cm^{-1}) 2927, 2860, 1733, 1667, 1155; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.88 (s, 1H), 3.00 (s, 3H, CH_3N), 2.97 (s, 3H, CH_3N), 2.57 (t, *J* = 6.3 Hz, 2H), 2.40 (t, *J* = 6.3 Hz, 2H), 2.04 (quin, *J* = 6.3 Hz, 2H).
18. *General procedure for the preparation of N-phenylbenzo[d]thiazol 2-amine* (**2a**): A mixture of 2-iodoaniline (1 mmol), phenyl isothiocyanate (1.2 mmol, 1.5 equiv), DABCO (2 mmol), Fe_3O_4@EDTA–Cu(II) (20 mg), and TBAB (10 mol %) was stirred in H_2O (3 mL) at 50 °C. After completion of the reaction as indicated by TLC, the catalyst was removed using an external magnet. Next, the mixture was extracted with EtOAc (2 × 5 mL). The combined EtOAc layer was then dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified over a column of silica gel (EtOAc/hexane, 1:4) to give the pure product **2a**.
19. *N-Phenylbenzo[d]thiazol-2-amine* (**2a**): White solid, isolated yield = 91%; mp 158–160 °C; IR (KBr, cm^{-1}) 3462, 1629; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.12–7.18 (m, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H).
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