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COMMUNICATION

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Nickel-catalyzed oxidative esterification of formamides with 1,3-dicarbonyl compounds under mild reaction conditions

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Synthesis of enol carbamates was achieved *via* nickel-catalyzed oxidative coupling of formamides with 1,3-dicarbonyl compounds in the presence of *tert*-butyl hydroperoxide at 40 °C. Various derivatives of enol carbamates were synthesized by this method in good to excellent yields.

KEYWORDS
1,3-Dicarbonyls, enol carbamates, nickel, oxidative coupling, TBHP

1 | INTRODUCTION

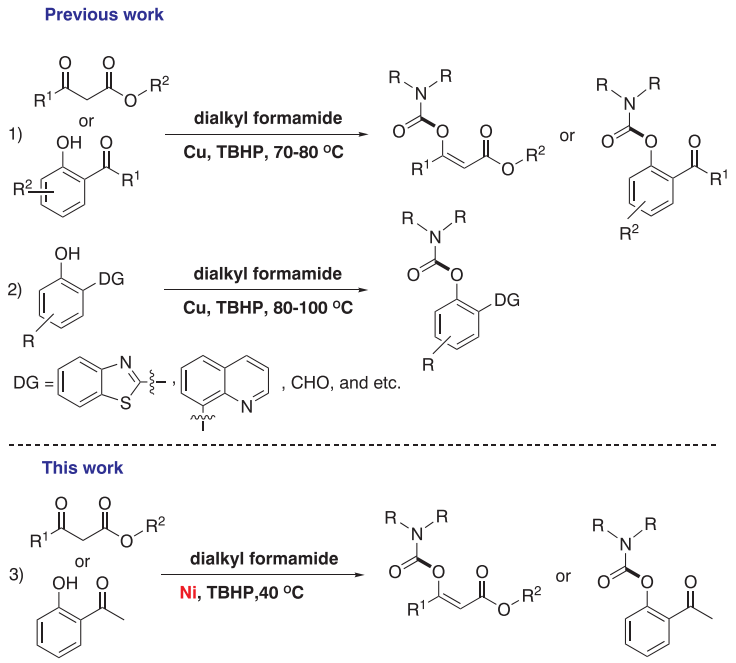
Carbamates are important motifs due to their pharmacological properties such as antibiotic, fungicide, insecticide, and herbicide.[1] Moreover, they are considered as significant synthetic intermediates and protecting groups in chemical industry.[2]

Traditionally, synthesis of these compounds is performed via the reaction of amines with phosgene or its derivatives, such as chloroformate,[3] dialkyl carbonates[4] or the reaction of alcohols with isocyanates.[5] However, regarding the toxicity of these reagents and the generation of various by-products, there is still room for the development of alternative methods.

Lately, cross-dehydrogenative coupling (CDC) has enhanced the efficiency of synthetic procedures leading to C-O bond formation.[6] These reactions enable one to synthesize molecules via shorter reaction routes and with higher atom-economy.[7]

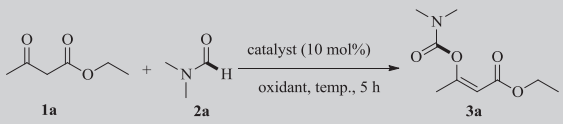
Copper-catalyzed CDC reaction of formamides with suitable precursors for the synthesis of carbamates has been well studied. In 2011, Reddy et al. reported the synthesis of enol carbamates and 2-carbonyl-substituted phenol carbamates *via* the oxidative coupling of formamides with *β*-dicarbonyl compounds or *ortho*-substituted phenolic compounds.[8] They performed these reactions in the presence of copper salts ($CuCl_2$ or $Cu(OAc)_2$) as the catalyst and TBHP as the oxidant at 80 °C (Scheme 1, Equation 1). Subsequently, Chang et al. conducted these reactions by employment of CuCl/TBHP system at 70 °C which resulted in the same products with excellent yields in a much shorter reaction time.[9] Moreover, copper-catalyzed oxidative coupling of formamides with salicylaldehydes has already been reported for the synthesis of carbamates (Scheme 1, Equation 2).[10]

Nickel, in its elemental form, has lower price than its d^{10}-block counterparts. Different oxidation states and small atomic radius which lead to short Ni–ligand bond lengths are among other distinctive features of nickel which justify its versatility.[11] Moreover, in contrast to palladium, facile accessibility of Ni(I) and Ni(III) oxidation states allows radical mechanisms in its reactions.[11] All these attributes make Ni a common catalyst in the area of cross-coupling reactions. [12] In this line of research, we have found that $NiCl_2$, a cheap and readily available salt, can be an effective substitute for copper in the synthesis of carbamates,



SCHEME 1 Different conditions for synthesis of carbamates via CDC reactions

TABLE 1 Screening optimum conditions[a]



1a 2a 3a

Entry	Catalyst (10 mol%)	Oxidant (mmol)	Temp (°C)	Yield (%)[b]
1	$NiCl_2.6H_2O$	TBHP (2)	RT	50
2	$Ni(OAc)_2.2H_2O$	TBHP (2)	RT	0
3	$Ni(NO_3)_2.6H_2O$	TBHP (2)	RT	0
4	$NiSO_4.6H_2O$	TBHP (2)	RT	0
5	$FeCl_2.4H_2O$	TBHP (2)	RT	0
6	$RuCl_3.xH_2O$	TBHP (2)	RT	0
7	$MnCl_2.4H_2O$	TBHP (2)	RT	0
8	$NiCl_2.6H_2O$	DTBP (2)	RT	0
9	$NiCl_2.6H_2O$	*m*CPBA (2)	RT	0
10	$NiCl_2.6H_2O$	H_2O_2 (2)	RT	0
11	$NiCl_2.6H_2O$	NaOCl (2)	RT	0
12	$NiCl_2.6H_2O$	Can (2)	RT	0
13	$NiCl_2.6H_2O$	TBHP (4)	RT	70
14	$NiCl_2.6H_2O$	TBHP (6)	RT	70
15	$NiCl_2.6H_2O$	TBHP (4)	40	90
16	$NiCl_2.6H_2O$	TBHP (4)	80	85
17	$NiCl_2.6H_2O$[c]	TBHP (4)	40	90
18	$NiCl_2.6H_2O$[d]	TBHP (4)	40	50
19	-	TBHP (4)	40	0
20	$NiCl_2.6H_2O$	-	40	0

[a]Reaction conditions: **1a** (1 mmol), **2a** (2 ml), 40 °C, 5 h, under air atmosphere. [b]Isolated yield; [c]20 mol% of catalyst was used; [d]5 mol% of catalyst was used.

since it has the aptitude to promote this reaction under milder conditions (Scheme 1, Equation 3).

2 | EXPERIMENTAL SECTION

2.1 | Chemicals, instrumentation and analysis

All reagents were purchased from commercial suppliers and used without further purification. Progress of reactions was monitored by thin layer chromatography while purification was effected by column chromatography, using silica gel (Merck 230–240 mesh). FT-IR spectra were obtained over the region 400–4000 cm^{-1} with NICOLET IR100 FT-IR with spectroscopic-grade KBr. ^{1}H–NMR and ^{13}C–NMR spectra were recorded on a Bruker Avance (DRX 300,400, or 500 MHz) in pure deuterated $CDCl_3$ solvent with tetramethylsilane (TMS) as internal standard.

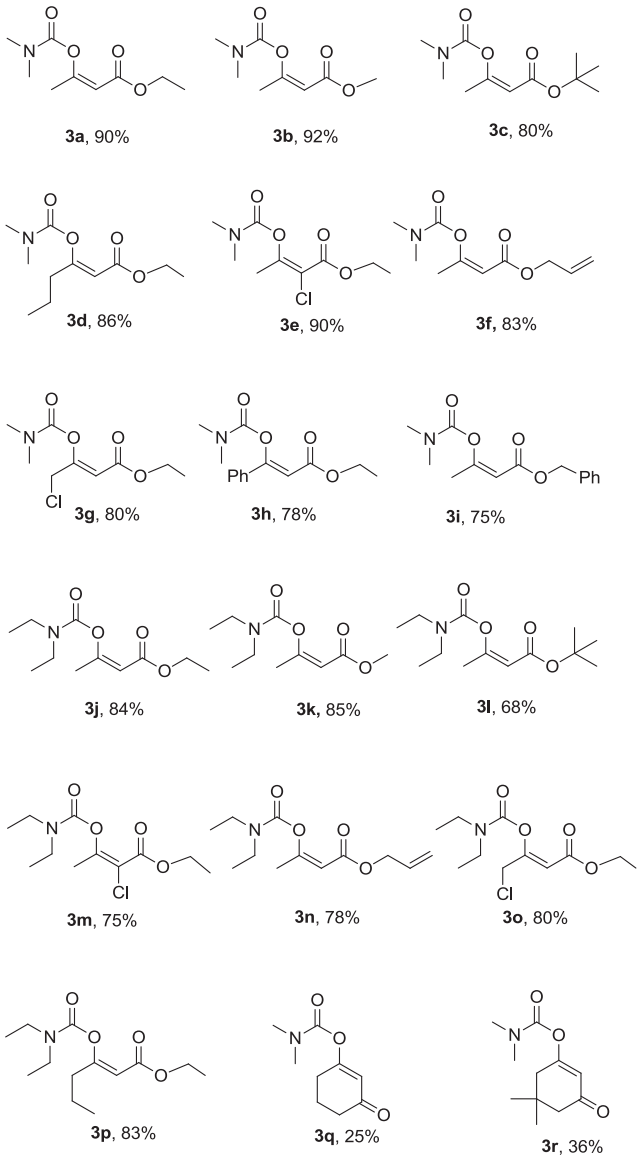


FIGURE 1 Substrate scope. Reaction conditions: β-diketone (1 mmol), TBHP (4 mmol), $NiCl_2.6H_2O$ (10 mol%), 40 °C, reaction time: 5 h; the yields refer to the isolated pure products

2.2 | General procedure for synthesis of carbamates (3a–r and 5a, 5b):

TBHP (70 wt% in water, 4 equiv) was added dropwise, with stirring over a period of 5 minutes, to a mixture of 1,3-dicarbonyl compound or 2-hydroxyacetophenone (1 mmol), $NiCl_2.6H_2O$ (24 mg, 10 mol%) and formamide (2 ml) at 40 °C. After stirring for five hours, water (10 ml) was added and then the reaction mixture was extracted with ethyl acetate (3 × 10 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product which was purified by column chromatography on silica gel (eluent: *n*-hexane-ethyl acetate 5: 1) to afford the desired product.

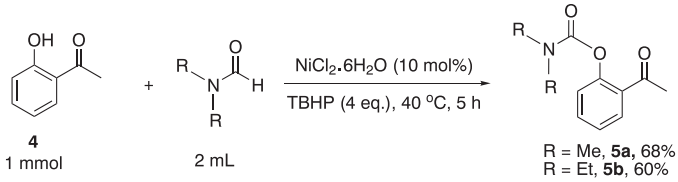
2.2.1 | General procedure for the esterification of 1,3-dicarbonyl compounds or 2-hydroxy acetophenone (7a–e and 8a–c)

TBHP (70 wt% in water, 4 equiv) was added dropwise, with stirring over a period of 5 min, to a mixture of 1,3-dicarbonyl compound or 2-hydroxyacetophenone (1 mmol), aldehyde (1.2 mmol), $NiCl_2.6H_2O$ (24 mg, 10 mol%) and DMSO (2 ml) at 40 °C. After stirring for ten hours, water (10 ml) was added and then the reaction mixture was extracted with ethyl acetate (3 × 10 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product which was purified by column chromatography on silica gel (eluent: *n*-hexane-ethyl acetate 5: 1) to afford the desired product.

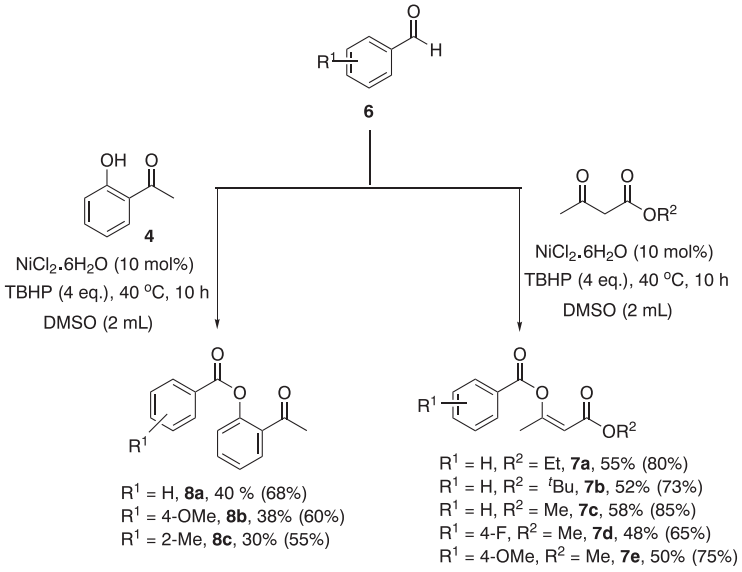
All the synthesized products were known and characterized by comparing spectral data with those of previously reported (see Supporting Information).[8–10,13]

3 | RESULTS AND DISCUSSION

To explore optimum conditions, the reaction of ethyl acetoacetate and DMF was selected as the model reaction. The first reaction was performed under the following conditions: ethyl acetoacetate (1 mmol), DMF (2 ml), TBHP (2 equiv.) as the oxidant, $NiCl_2.6H_2O$ (10 mol%) as the catalyst at room temperature. Under these conditions, enol carbamate **3a** was obtained in 50% yield (Table 1, entry 1). Other Ni salts such as $Ni(OAc)_2.2H_2O$, $Ni(NO_3)_2.6H_2O$, and $NiSO_4.6H_2O$ failed to promote this transformation (Table 1, entries 2–4). Further investigation revealed that attempts to achieve the desired product by the use of chloride salts of Fe, Ru, and Mn were futile



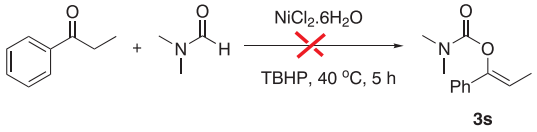
SCHEME 2 Oxidative esterification of 2-hydroxyacetophenone with formamides



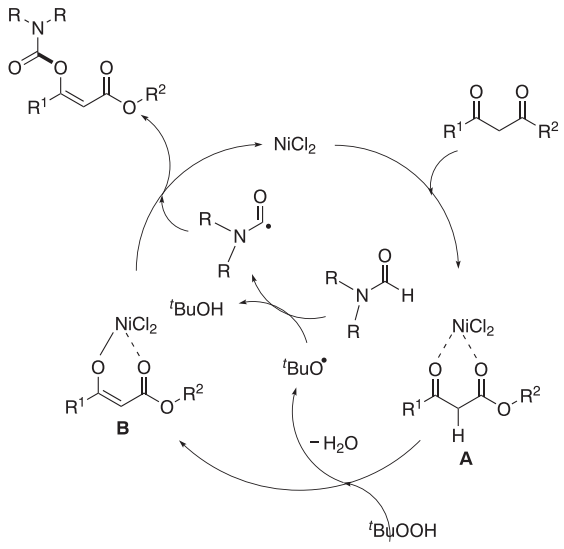
SCHEME 3 Oxidative esterification of aldehydes with β-diketones or 2-hydroxyacetophenone. Values in pranteses refer to perform the reactions at 80 °C

(Table 1, entries 5–7). Next, the effect of oxidants on the yield of the product was taken into account. With this aim in mind, the reaction was carried out in the presence of several oxidizing reagents, such as DTBP, *m*CPBA, H_2O_2, NaOCl, and CAN, but in neither case was carbamate formed (Table 1, entries 8–12). Fortunately, when the amount of the oxidant increased up to 4 equivalents, the yield was raised to 70% (Table 1, entry 13). However, further build-up of the oxidant amount brought about a negligible change in the yield (Table 1, entry 14). In the next step, we investigated the temperature influence. To this end, the temperature rose to 40 °C which improved the reaction efficiency (Table 1, entry 15), but additional increase in the temperature led to a drop of yield (Table 1, entry 16). Then, we conducted the reaction in the presence of 20 mol% of the catalyst under which the yield remained almost unchanged, while reducing its amount to 5 mol%, decreased the efficiency to 50% (Table 1, entries 17 and 18). It is also noteworthy that in the absence of the catalyst or the oxidant, no product was formed (Table 1, entries 19 and 20) assuring that their presence is crucial for promotion of this reaction.

After optimization, in order to extend the scope of this reaction, a wide range of 1,3-dicarbonyl compounds were reacted with *N*,*N*-dialkyl formamides under optimum conditions which in most cases furnished the desired enol carbamates in high yields. The results are shown in Figure 1. In accordance with the previously reported



SCHEME 4 Unsuccessful esterification of propiophenone with DMF



SCHEME 5 Proposed mechanism

results, the nature of the 1,3-dicarbonyl compounds and dialkyl formamides did not have any significant influence on the reactivity. It should be noted that the reason

behind the lower yield of 1,3-cyclohexadione carbamates (**3q** and **3r**) is perhaps due to the lack of binding capacity of cyclic *β*-diketones to the metal in a bidentate fashion.[9]

Encouraged by these results, we then replaced *β*-dicarbonyls with 2-hydroxyacetophenone **4** which has structural similarities to the enol tautomer of the diketone moiety. To our delight, when reacted with dialkylformamides, the corresponding carbamates were obtained in acceptable yields under the same conditions (Scheme 2).

In another attempt, the reaction of aldehydes with *β*-diketones or 2-hydroxyacetophenone, which has already been conducted by a copper catalyst,[13] was investigated in which Ni proved to be gratifyingly efficacious. Also, when the temperature rose to 80 °C even better results were obtained. (Scheme 3).

Although the exact reaction mechanism still remains unclear, the reaction may proceed in a similar mode to Cu-catalyzed esterification as previously reported.[8–10,13,14] The reaction was completely suppressed when 1.5 equiv. of TEMPO was added to the model reaction confirming that it proceeded through a radical pathway. As has already been taken into consideration,[15] dicarbonyl compounds have an aptitude to coordinate metals and set the scene for implementation of this reaction. To support this hypothesis, when the propiophenone was subjected to the reaction conditions, the product **3 s** was not formed (Scheme 4). This indicates the importance of the adjacent carbonyl group for carbamate formation.

Accordingly, we proposed a mechanism which is depicted in Scheme 5. Presumably, at the first stage complex (**A**) is formed through the reaction of *β*–dicarbonyl with the nickel salt. Treatment of this complex with TBHP produces complex (**B**) and a *tert*-butoxyl radical. *Tert*-Butoxyl radical then abstracts a hydrogen radical from formamide giving rise to the corresponding radical. This radical, then, reacts with nickel complex (**B**) affording the desired carbamate and Ni(II) chloride which returns to the catalytic cycle.

4 | CONCLUSIONS

In conclusion, we have described the first example of a Ni-catalyzed oxidative esterification of 1,3-dicarbonyl compounds or 2-hydroxyacetophenone with formamides toward the synthesis of enol carbamates with TBHP as an environmentally benign oxidant. $NiCl_2$, as a cheap and readily available nickel salt, is able to catalyze this transformation effectively under mild reaction conditions. Various enol carbamates were synthesized in good to excellent yields. Oxidative coupling of benzaldehyde and its derivatives with *β*–dicarbonyls was also tested which resulted in the satisfactory yields of the corresponding products. Control experiments showed that the coordination of dicarbonyl compounds with Nickel played an important role in the reaction mechanism.

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