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Metal free oxidative coupling of aryl formamides with alcohols for the synthesis of carbamates†

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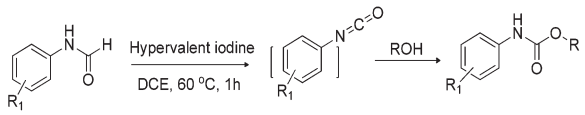
A direct transformation of *N*-aryl formamides to the corresponding carbamates *via* the formation of isocyanate intermediates is achieved in good yields using hypervalent iodine as an oxidant.

Organic carbamates are synthetically highly useful compounds having widespread utility in areas such as pharmaceuticals,[1] agrochemicals,[2] and polymers[3] and as valuable protecting groups in peptide chemistry.[4] Typically, carbamates are synthesized by reacting suitable alcohols with isocyanates, which in turn are prepared from phosgene.[5] However, to overcome the issues associated with phosgene chemistry, considerable attention has been paid in the recent past to developing efficient and safer methodologies for carbamate synthesis.[6] As a result many methods have been made available for their synthesis, including oxidative and reductive carbonylation of amines and nitroaromatics,[7] the utilization of CO_2,[8] application of metal catalyzed cross couplings of isocyanate anions and the various rearrangement reactions.[9]

In recent years oxidative couplings involving C–H bond activations have been recognized as useful strategies in synthetic organic chemistry and the importance of these approaches are well documented in several recent reviews.[10] Though the formamides are traditionally used as solvents and also as a source of CO, Me_2N, Me_2NCO, and oxygen for various organic transformations,[11] the synthetic utility of these formamides in coupling reactions under oxidative conditions was exploited only in recent investigations. For example, it has been shown that formamide can act as a source of amide or amine in amidation reactions.[12] Similarly, direct synthesis of α-ketoamides was achieved from methyl ketones and dialkylformamides using *tert*-butylhydroperoxide (TBHP) as an oxidant and nBu_4NI as a catalyst.[13]



Scheme 1 Carbamate synthesis *via* isocyanate intermediate from *N*-aryl formamides.

Our group has been working on oxidative couplings using metal and non-metal catalysts over the last couple of years.[14] During these investigations, we have shown the direct coupling of formamides with phenols and β-keto esters under oxidative conditions.[15] While the method allowed accessing the phenol carbamates, the substrate scope was limited to 2-carbonyl substituted derivatives. Moreover use of formamide in large excess as both solvent and reagent further limits the application of this useful reaction. In order to expand the scope of the formamides especially with aromatic formamides, we explored the other possibilities. Since hypervalent iodine compounds are extensively used for carbamate synthesis in Hofmann-type rearrangements, where the isocyanate is the key intermediate,[16] we have chosen these oxidants for the present work. Moreover, we anticipated that a direct transformation of formamides to isocyanates could be much more useful for making carbamates (Scheme 1). Although the possibility of direct conversion of *N*-arylformamides to corresponding carbamates using lead(IV) acetate was reported by Leardini and co-workers,[17] to the best of our knowledge hypervalent iodine reagents were not utilized for this direct transformation.

First, we have investigated the formation of carbamate between *N*-phenyl formamide and *n*-butanol under different reaction conditions, and results are summarized in Table 1. The use of (diacetoxyiodo)benzene as an oxidant resulted in a maximum yield of 25% in dichloroethane at an elevated temperature (Table 1, entry 4). Inferior results are observed when the reaction is carried out with other solvents and copper catalysts (see other entries in Table 1). However, a sharp rise in yield (82%) was observed when [bis(trifluoroacetoxy)iodo]benzene was used as an oxidant (Table 1, entry 8).

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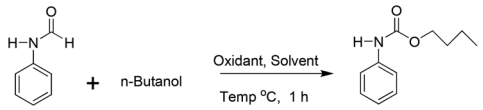
Table 1 Optimization studies of *N*-aryl carbamate synthesis for the reaction between *N*-phenyl formamide and *n*-butanol[a]



Entry	Oxidant	Solvent	Temp./°C	Isolated yield [%]
1	$PhI(OAc)_2$	DCM	rt	NR
2	$PhI(OAc)_2$	DCM	40	15
3	$PhI(OAc)_2$	THF	60	NR
4	$PhI(OAc)_2$	DCE	60	25
5	TBHP, $Cu(OAc)_2$	DCE	60	5
6	H_2O_2, $Cu(OAc)_2$	DCE	60	NR
7	$PhI(OCOCF_3)_2$	DCE	rt	40
8	$PhI(OCOCF_3)_2$	DCE	60	82

[a] Reaction conditions: *N*-phenyl formamide (1 mmol), *n*-butanol (5 mmol), dichloroethane (3 mL, solvent), oxidant (1 mmol), 60 °C, MS 4 Å, N_2, 1 h.

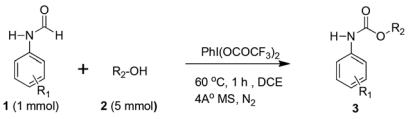
Moreover, a drop in yields is also observed when the reaction is carried out either taking lower amounts of alcohols or in the absence of molecular sieves. Performing the reactions for longer reaction times does not improve the yield; in contrast we observed some decomposition of the product.

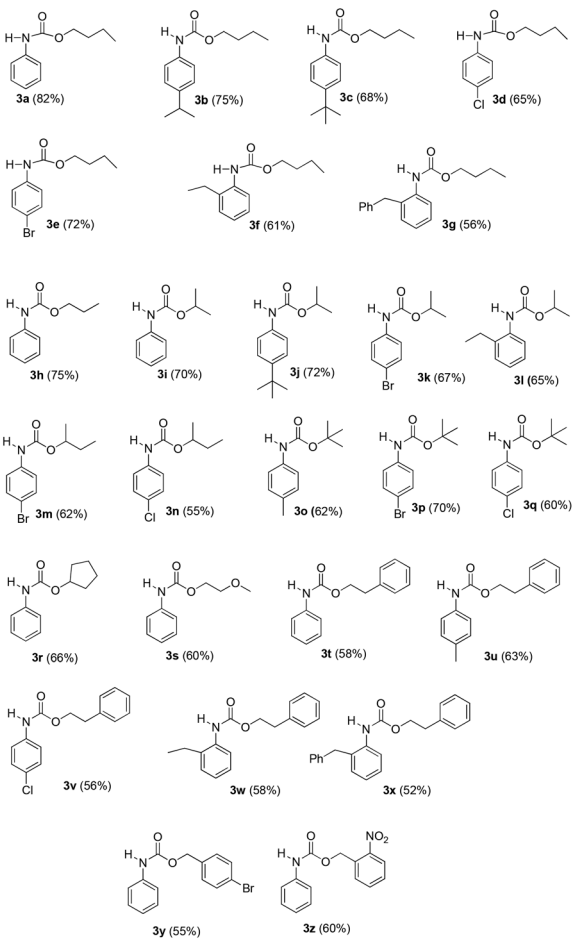
With these optimizations, we looked at the scope of the reaction with different *N*-aryl formamides and alcohols (Table 2).[18] First we have screened with *n*-butanol with different formamides and found that both electron donating and withdrawing groups on the phenyl group work very well for this reaction, providing the carbamate product in 65–82% yield (Table 2, **3a–3e**). However, a small decrease in yield was observed for the electron withdrawing substrate with respect to donating analogues. Similarly, substitution at *ortho*-position with ethyl- and benzyl- groups on aryl formamide has little influence on yields of the product (Table 2, **3f** and **3g**).

Further investigations were carried out with different alcohols and formamides, and results are shown in Table 2. Variation of alcohols *viz.* *n*-propanol, *iso*-propanol, *iso*-butanol, *tert*-butanol and cyclo-pentanol provided the corresponding carbamates in good yields (Table 2, **3h–3r**). Then we looked at other alcohols such as 2-methoxyethanol and 2-phenylethanol, and invariably we observed moderate to good yields of the desired carbamate products (Table 2, **3s–3x**). Finally to expand the scope of alcohols, formamides are treated with phenols and benzyl alcohols. In the case of benzyl alcohols, a moderate yield of the carbamate products (Table 2, **3y** and **3z**) are isolated. On the other hand, no product was observed with simple phenol.

Based on previously reported mechanistic studies of aryl carbamates using lead(IV) acetate,[17] we propose that the isocyanate formation is the key step in this reaction also (Scheme 1). Further, isocyanate formation could also be possible from amidoiodane intermediates, which are proposed in Hofmann rearrangement of amides using hypervalent iodine reagents (see ESI† for mechanism).[16b] Moreover, GC-MS analysis of the reaction mixture in the absence of alcohols clearly reveals the formation of isocyanate intermediates.

Table 2 Direct synthesis of *N*-aryl carbamates (**3**) from *N*-aryl formamides (**1**) and alcohols (**2**)[a]





[a] Reaction conditions: *N*-arylformamide (**1**) (1 mmol), alcohol (**2**) (5 mmol), dichloroethane (3 mL, solvent), oxidant (1 mmol), 60 °C, MS 4 Å, N_2, 1 h.

Conclusions

In summary, we have reported a mild and efficient procedure for the synthesis of *N*-aryl carbamates by a direct transformation of *N*-aryl formamides. Two important features: (i) accessibility of the formamides from the commercially available amines by various catalytic procedures and (ii) the direct transformation of formamides to carbamates *via* isocyanate formation, may provide the present reaction a synthetic advantage over Hofmann type rearrangements, where amides

are often used. Moreover, isocyanate intermediate from formamides can be readily utilized for various organic transformations, which we are currently investigating in our laboratory.

Acknowledgements

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18 General procedure for the synthesis of *N*-aryl carbamates: in a reaction vessel 1 mmol of *N*-aryl formamide was dissolved in 3 mL of dichloroethane solvent, and slowly added the [bis(trifluoroacetoxy)iodo]benzene (oxidant, 1 mmol) to the solution with stirring over a period of 2 minutes in the presence of molecular sieves (4 Å) under a nitrogen atmosphere. Then 5 mmol of alcohol was added to the above reaction mixture and the temperature was increased to 60 °C and stirred for one hour. The reaction was monitored by thin layer chromatography. After completion of the reaction, the resulting solution was cooled to room temperature. The reaction mixture was then filtered through a silica gel bed using ethyl acetate and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a petroleum ether/ethyl acetate mixture used as an eluent to afford the corresponding products. The products were confirmed by ^{1}H, ^{13}C NMR, IR and mass spectroscopic analysis. **Butyl phenylcarbamate:** (compound **3a**): (**Isolated yield** = 82%): **IR** cm^{-1}: 3372, 2940, 1725, 1532, 1297, 1078, 745, 632. **^{1}H NMR** δ (500 MHz, $CDCl_3$): 7.38 (d, J = 7.6 Hz, 2H), 7.30 (t, J = 7.4 Hz, 2H), 7.03 (t, J = 7.4 Hz, 1H), 6.74 (br, 1H), 4.16 (t, J = 6.7 Hz, 2H), 1.67–1.61 (m, J = 7.1 Hz, 2H), 1.43–1.37 (m, J = 7.6 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H). **^{13}C NMR** δ (75 MHz, $CDCl_3$): 153.7, 137.9, 128.9, 123.2, 118.5, 65.0, 30.8, 19.0, 13.6. **MS (ESI):** m/z = 216 $(M + Na)^+$, **HRMS:** ESI $(M + H)^+$ m/z calcd for $C_{11}H_{16}O_2N$ $(M + H)^+$ = 194.11810, found = 194.11717.