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N-Heterocyclic Carbene Catalyzed Oxidative Coupling of Aldehydes with Carbodiimides under Aerobic Conditions: Efficient Synthesis of *N*-Acylureas

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ABSTRACT

The oxidative coupling reaction of aldehydes with *N,N*′-disubstituted carbodiimides catalyzed by *N*-heterocyclic carbenes under aerobic conditions has been achieved. This reaction gives the corresponding *N*-acylurea derivatives in good to high yields. Various kinds of aldehydes including aliphatic ones and carbodiimides are applicable to this reaction.

The broad range of applications for *N*-heterocyclic carbenes (NHCs) in organic synthesis has been demonstrated in the years since Bertrand, Arduengo, et al. reported the first stable nucleophilic carbene around 1990.[1,2] The NHC-catalyzed inversion of the normal reactivity of aldehydes, via so-called *umpolung*, has become an area of intense research, providing the basis for a wide range of organic transformations. The umpolung reactivity of NHCs has been investigated in many organic transformations employing various kinds of acyl anion acceptors.[1,3] Recently, the utility of NHCs has been extended to redox reactions[4] and oxidation reactions where NHC was used in combination with molecular oxygen,[5] carbon dioxide,[6] or with an organic oxidant.[7]

N-Acylureas have long attracted significant attention due to their biological activities, i.e., analgesic, anti-inflammatory, anthelmintic, antifungal, and larvicidal properties.[8] In the area of natural products, cabergoline was found to be a potent long-lasting prolactin inhibitor.[9] The efficacy of cabergoline has been evaluated in many clinical trials.[10] In addition, it has been known that *N*-acylureas inhibit the growth and reproduction of the fall army worm and

(1) Recent reviews: (a) Grossmann, A.; Enders, D. *Angew. Chem., Int.Ed.* **2012**, *51*, 314–325. (b) Vreese, R. D.; D'hooghe, M. *Beilstein J. Org. Chem.* **2012**, *8*, 398–402. (c) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522. (d) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53–57. (e) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Soc.* **2011**, *44*, 1182–1195. (f) Hirano, K.; Piel, I.; Glorius, F. *Chem. Lett.* **2011**, *40*, 786–791. (g) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336–5346. (h) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857–7870. (i) Zeitler, K. *Ernst Schering Found. Symp. Proc* **2007**, *2*, 183–206. (j) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5665. (k) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988–3000. (l) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506–7510. (m) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632–2634. (n) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326–1328.

(2) (a) Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 6940–6952. (b) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021–1023. (c) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361–363. (d) Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463–6466. (e) Ukai, T.; Tanaka, R.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296–300.

(3) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691–2698.

(4) (a) Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373–375. (b) Sarkar, S. D.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266–9269. (c) Guin, J.; Sarkar, S. D.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727–8730. (d) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371–374. (e) Sohn, S. S.; Bode, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 6021–6024. (f) Zeitler, K. *Org. Lett.* **2006**, *8*, 637–640. (g) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908. (h) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406–16407. (i) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371.

(5) (a) Chiang, P.-C.; Bode, J. W. *Org. Lett.* **2011**, *13*, 2422–2425. (b) Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228–2231. (c) Maji, B.; Vedachalan, S.; Ge, X.; Cai, S.; Liu, X.-W. *J. Org. Chem.* **2011**, *76*, 3016–3023.

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house fly.[11] Very recently, Ruat reported *N*-acylureas have acted as inhibitors of hedgehog signaling.[12] For these reasons, it is very important to develop an efficient synthesis of *N*-acylurea derivatives. There are various examples in the older literature of the formation of *N*-acyl derivatives from reactions of carbodiimides with carboxylic acids in the presence of bases.[13] In 1995, reactions of substituted benzoic acids with *N,N′*-dicyclohexylcarbodiimide (DCC) in the presence of $[Bu_3NH][ClO_4]/[Bu_3N]$ buffer were shown to afford *N*-acylurea derivatives, and several improved reactions of DCC with carboxylic acids have been reported.[14] Recently, Srivastava reported the reaction of benzoic acid derivatives and *N,N′*-disubstituted carbodiimides under solvent-free conditions in a microwave oven in 2007.[15] As far as we know, there are no examples of the catalytic synthesis of *N*-acylureas from aldehydes and *N,N′*-disubstituted carbodiimides. Herein, we present the first report on a highly effective coupling reaction of aldehydes with *N,N′*-disubstituted carbodiimides catalyzed by NHC under aerobic conditions using several *N*-heterocyclic carbene precursors (Figure 1).

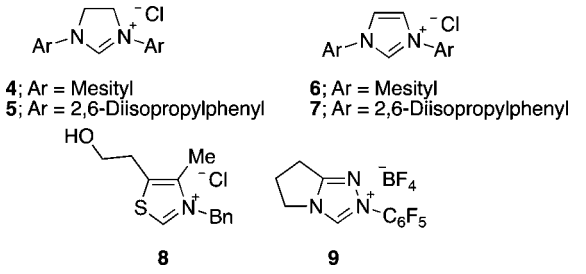
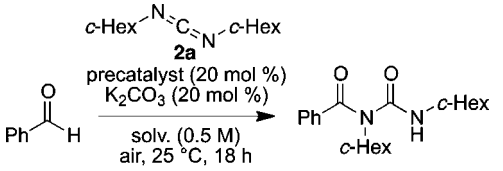


Figure 1. Structures of *N*-heterocyclic carbene precursors.

We began the optimization studies using benzaldehyde (**1a**) and *N,N′*-dicyclohexylcarbodiimide (**2a**) as a model substrate (Table 1).

Table 1. Effect of Precatalysts and Solvents



entry	precatalyst	solv.	yield (%)
1	**4**	CH_2Cl_2	65
2	**5**	CH_2Cl_2	23
3	**6**	CH_2Cl_2	4
4	**7**	CH_2Cl_2	6
5	**8**	CH_2Cl_2	10
6	**9**	CH_2Cl_2	29
7	**4**	THF	62
8	**4**	toluene	35
9	**4**	MeCN	73
10[a]	**4**	MeCN	88
11[a,b]	**4**	MeCN	93
12[a,b]	–	MeCN	nr

[a] Concentration was 1.0 M. [b] 1.2 equiv of **1a** and 1.0 equiv of **2a** were used. Yield is calculated on the basis of **2a**.

The initial experiments on the reaction between **1a** and **2a** under aerobic conditions were performed using 20 mol % of NHC precatalyst **4** and potassium carbonate (K_2CO_3) as a base to generate the carbene catalyst in dichloromethane (CH_2Cl_2). The corresponding *N*-acylurea **3aa** was obtained in 65% yield after 18 h. Encouraged by this result, further studies were carried out by employing 20 mol % of **5**–**9** as a precatalyst (entries 2–6). The reaction proceeded in all cases; however, the reactivities were very low, affording the product **3aa** in low yields. From these results, precatalyst **4** was found to be more active than the other precatalysts **5**–**9**. The reaction proceeded smoothly in both CH_2Cl_2 and tetrahydrofuran (THF) to afford **3aa** in good yields (entries 1 and 7). When toluene was used as a solvent, the reaction was sluggish to afford **3aa** in 35% yield (entry 8). Acetonitrile (MeCN) was the most effective solvent for this reaction, affording **3aa** in 73% yield (entry 9). When the reaction was carried out at higher concentration (1.0 M), the product **3aa** was obtained in 88% yield (entry 10). A significant increase in yield was observed when 1.2 equiv of **1a** and 1.0 equiv of **2a** were used, and the product **3aa** was isolated in 93% yield (entry 11). In the absence of the precatalyst **4**, the reaction did not proceed at all (entry 12).

Under the optimized reaction conditions using the highly active precatalyst **4**, the scope of the catalytic oxidative coupling was explored with various aromatic and aliphatic aldehydes (Table 2). We were delighted to find that our

(6) (a) Gu, L.; Zhang, Y. *J. Am. Chem. Soc.* **2010**, *132*, 914–915. (b) Nair, V.; Varghese, V.; Paul, R. R.; Jose, A.; Sinu, C. R.; Menon, R. S. *Org. Lett.* **2010**, *12*, 2653–2655.

(7) (a) Iwahana, S.; Iida, H.; Yashima, E. *Chem.—Eur. J.* **2011**, *17*, 8009–8013. (b) Sarkar, S. D.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190–1191. (c) Rose, C. A.; Zeitler, K. *Org. Lett.* **2010**, *12*, 4552–4555. (d) Sarkar, S. D.; Studer, A. *Org. Lett.* **2010**, *12*, 1992–1995. (e) Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102–3109. (f) Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron Lett.* **2008**, *49*, 4003–4006. (g) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331–4334.

(8) (a) Ranise, A.; Schenone, S.; Bruno, O.; Bondavalli, F.; Filippelli, W.; Falcone, G.; Rivaldi, B. *Il Farmaco* **2001**, *56*, 647–657. (b) Arbuzov, B. A.; Fedotova, N. R.; Zobovi, N. N.; Nazyrova, A. Z.; Anan'ev, E. V.; Gorbunov, S. M. *Khim. Farm. Zhl.* **1989**, *23*, 682–683. (c) Karmouta, M. G.; Miocque, M.; Derdour, A.; Gayral, P.; Lafont, O. *Eur. J. Med. Chem.* **1989**, *24*, 547–549. (d) Nakagawa, Y.; Iwamura, H.; Fujita, T. *Pestic. Biochem. Physiol.* **1985**, *23*, 7–12.

(9) Brambilla, E.; Di Salle, E.; Briatico, G.; Mantegani, S.; Temperilli, A. *Eur. J. Med. Chem.* **1989**, *24*, 421–426.

(10) (a) Rinne, U. K.; Bracco, F.; Chouza, C.; Dupont, E.; Gershanik, O.; Masso, J. F. M.; Montastruc, J. L.; Marsden, C. D. *Drugs* **1998**, *55* (Suppl I), 23–30. (b) Hutton, J. T.; Koller, W. C.; Ahlskog, J. E.; Pahwa, R.; Hurtig, H. I.; Stern, M. B.; Hiner, B. C.; Lieberman, A.; Pfeiffer, R. F.; Rodnitzky, R. L.; Waters, C. H.; Muenter, M. D.; Adler, C. H.; Morris, J. L. *Neurology* **1996**, *46*, 1062–1065. (c) Lera, G.; Vaamonde, J.; Rodriguez, M.; Obeso, J. A. *Neurology* **1993**, *43*, 2587–2590.

(11) DeMilo, A. B.; Ostromecky, D. M.; Chang, S. C.; Redfern, R. E.; Fye, R. L. *J. Agri. Food Chem.* **1978**, *26*, 164–166.

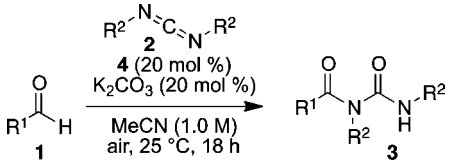
(12) Solinas, A.; Faure, H.; Roudaut, H.; Traiffort, E.; Schoenfelder, A.; Mann, A.; Manetti, F.; Taddei, M.; Ruat, M. *J. Med. Chem.* **2012**, *55*, 1559–1571.

(13) DeTar, D. F.; Silverstein, R. *J. Am. Chem. Soc.* **1966**, *88*, 1013–1019.

(14) Ślebioda, M. *Tetrahedron* **1995**, *51*, 7829–7834.

(15) Neves Filho, R. A. W.; de Oliveira, R. N.; Srivastava, R. M. *J. Braz. Chem. Soc.* **2007**, *18*, 1410–1414.

Table 2. Scope of Aldehydes and Carbodiimides

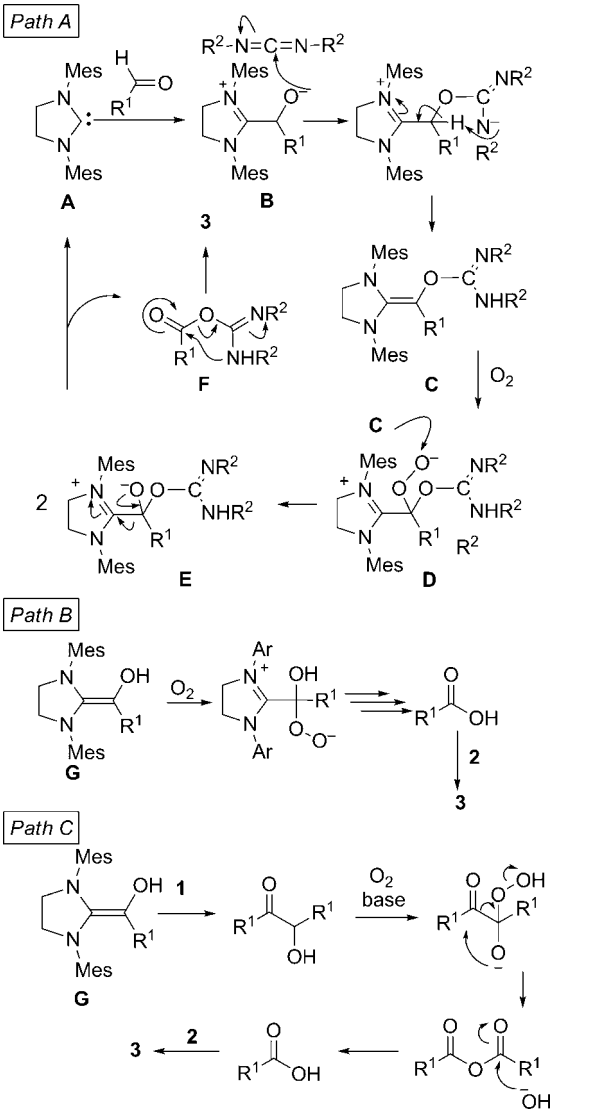


entry[a]	R^1	R^2	yield (%)
1	C_6H_5 (**1a**)	*c*-Hex (**2a**)	93 (**3aa**)
2	2-naphthyl (**1b**)	*c*-Hex (**2a**)	91 (**3ba**)
3[b]	2-BrC_6H_4 (**1c**)	*c*-Hex (**2a**)	83 (**3ca**)
4[b]	2-MeC_6H_4 (**1d**)	*c*-Hex (**2a**)	84 (**3da**)
5[b]	2-$MeOC_6H_4$ (**1e**)	*c*-Hex (**2a**)	97 (**3ea**)
6	2-ClC_6H_4 (**1f**)	*c*-Hex (**2a**)	80 (**3fa**)
7	3-ClC_6H_4 (**1g**)	*c*-Hex (**2a**)	85 (**3ga**)
8	4-ClC_6H_4 (**1h**)	*c*-Hex (**2a**)	88 (**3ha**)
9	4-BrC_6H_4 (**1i**)	*c*-Hex (**2a**)	90 (**3ia**)
10	4-$CF_3C_6H_4$ (**1j**)	*c*-Hex (**2a**)	83 (**3ja**)
11[b]	4-MeC_6H_4 (**1k**)	*c*-Hex (**2a**)	96 (**3ka**)
12[b]	4-$MeOC_6H_4$ (**1l**)	*c*-Hex (**2a**)	70 (**3la**)
13	2-pyridyl (**1m**)	*c*-Hex (**2a**)	86 (**3ma**)
14[b]	2-furyl (**1n**)	*c*-Hex (**2a**)	70 (**3na**)
15[b]	2-phenylethenyl (**1o**)	*c*-Hex (**2a**)	81 (**3oa**)
16	2-phenylethynyl (**1p**)	*c*-Hex (**2a**)	-[c]
17[b]	2-phenylethyl (**1q**)	*c*-Hex (**2a**)	81 (**3qa**)
18	*c*-Hex (**1r**)	*c*-Hex (**2a**)	86 (**3ra**)
19[b]	*t*-Bu (**1s**)	*c*-Hex (**2a**)	38 (**3sa**)
20	C_6H_5 (**1a**)	*i*-Pr (**2b**)	79 (**3ab**)
21	C_6H_5 (**1a**)	Et (**2c**)	76 (**3ac**)
22[d]	C_6H_5 (**1a**)	*t*-Bu (**2d**)	43 (**3ad**)
23[b]	C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**2e**)	21 (**3ae**)

[a] 1.2 equiv of **1** and 1.0 equiv of **2** were used. [b] Reaction time was 45 h. [c] Reaction was messy. [d] Reaction time was 90 h.

catalytic system was applicable to a wide range of aldehydes when the reactions were conducted using 20 mol % of **4** and 20 mol % of K_2CO_3 in MeCN at room temperature under aerobic conditions. 2-Naphthaldehyde (**1b**) was found to be a good substrate, and the product **3ba** was obtained in 91% yield (entry 2). Although the reaction times were longer, *ortho*-substituted benzaldehydes **1c**−**e** were applicable to this reaction (entries 3−5). We examined substituted benzaldehydes bearing electron-withdrawing groups. Regarding the substitution pattern of the benzaldehydes, the 2-, 3-, and 4-chloro substituents were all tolerated, furnishing the corresponding *N*-acylureas in high yields (entries 6−8). Similar reactivities were observed with 4-bromo and 4-(trifluoromethyl)benzaldehydes (**1i** and **1j**) (entries 9 and 10). The reactions of relatively deactivated 4-methylbenzaldehyde (**1k**) and 4-methoxybenzaldehyde (**1l**) were sluggish; however, improved chemical yields were realized after 45 h (entries 11 and 12). Heteroaromatic aldehydes, 2-pyridinecarboxaldehyde (**1m**) and furfural (**1n**) were also applicable to this reaction, although furfural (**1n**) showed lower reactivity (entries 13 and 14). Cinnamaldehyde (**1o**) was also an effective substrate to afford the product **3oa** in 81% yield (entry 15), however, phenylpropargyl aldehyde (**1p**) was not effective in this reaction (entry 16). Fortunately, aliphatic aldehydes **1q**−**s** were also useful in this

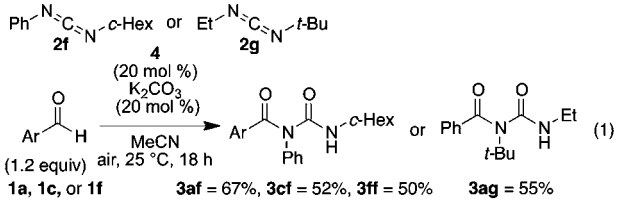
Scheme 1. Plausible Reaction Mechanism

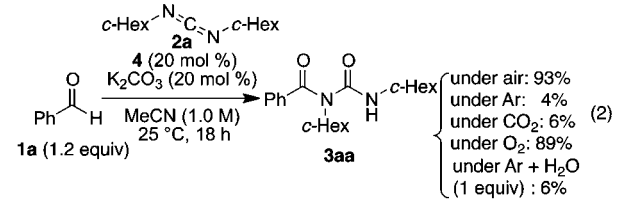


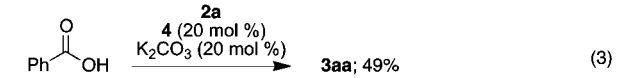
reaction without any production of aldol compounds (entries 17 and 18). In the case of pivalaldehyde (**1s**), the reactivity was very low, probably due to the steric bulkiness of the substrate (entry 19). The reactivity toward various *N,N*′-disubstituted carbodiimides **2b**−**e** using benzaldehyde (**1a**) was examined next by treatment of 20 mol % of precatalyst **4** and K_2CO_3. *N,N*′-Dialkylcarbodiimides (R^2 = *i*-Pr, Et) **2b** and **2c** were good substrates for this reaction to afford the corresponding products (entries 20 and 21). The only exception was *N,N*′-di-*tert*-butylcarbodiimide (**2d**) in which the reaction was very sluggish (entry 22). In the case of aromatic substituted carbodiimide **2e**, lower reactivity was observed to afford the product in 21% yield after 45 h (entry 23). In the case of the reactions of **1a**, **1c**, and **1f** with unsymmetrical carbodiimides **2f** and **2g** under optimized reaction conditions, the reaction proceeded regioselectively to afford the product **3af**, **3cf**, **3ff**, and **3ag** as a sole product in moderate yield (eq 1).

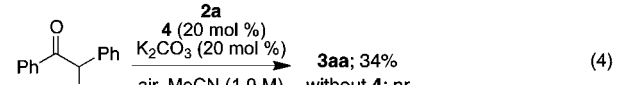
To gain mechanistic insight into this reaction, a series of control experiments was rationally designed and

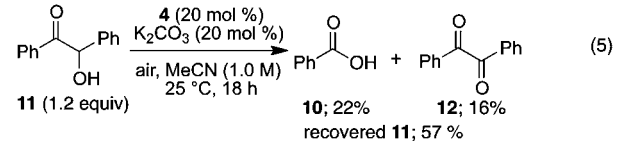
performed (eqs 2−6). The first set of experiments was conducted in order to determine the source of the oxygen atom in this reaction (eq 2). Reaction of **1a** under an argon or a carbon dioxide atmosphere resulted in drastically decreased conversion, while replacement with air or oxygen dramatically improved the yield of **3aa**. The introduction of water (1.0 equiv) under an argon atmosphere did not show a significant effect in this reaction. These results indicate that oxygen plays an important role as the source of oxygen in this transformation.

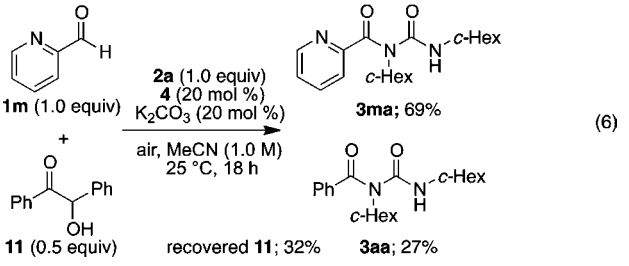












The reaction of benzoic acid (**10**) with **2a** proceeded even in the absence of precatalyst **4**; however, reactivity was lower (eq 3). Han and Yang recently reported the oxidation of benzoin (**11**) to benzoic acid (**10**) in the presence of sodium hydride as a base under oxygen atmosphere.[16b] When benzoin (**11**) was used instead of **1a** under optimized reaction conditions, the product **3aa** was obtained in 34% yield (eq 4). Benzoic acid (**10**) was also obtained in 22% yield in the absence of carbodiimide **2a** (eq 5).[16] In addition, the reaction of **1m** and **2a** in the presence of **11** (0.5 equiv) and precatalyst **4** afforded the mixture of **3ma** and **3aa** in 69% and 27%, respectively (eq 6). On the other hands, we confirmed that benzoin was obtained only in 13% yield after 18 h when the reaction of **1a** was carried out in the absence of **2a**.

On the basis of these results, a plausible mechanism for this transformation is proposed as shown in Scheme 1. Initially, the addition of carbene **A** generated in situ from **4** to the aldehyde forms intermediate **B**. Next, the harder oxygen anion[17] rather than the normal acyl anion equivalent (**G**, shown in paths B and C) attacks the carbodiimide, followed by proton transfer to afford the electron-rich enaminol ether **C**. The intermediate **C** may attack an electrophilic dioxygen to afford the hydroperoxide anion **D**.[18] Then, another enaminol ether **C** may react with intermediate **D** to generate two molecules of **E**, which subsequently eliminates the carbene catalyst **A** to afford the carboxylate intermediate **F**.[19] Finally, acyl transfer leads to the corresponding *N*-acylurea **3** (path A). Based on eqs 3−6, the carboxylic acid generated from the oxidation of the Breslow intermediate **G** and/or benzoin **11** may be involved in this reaction (paths B and C) However, we assume that path A is the predominant pathway due to the low reactivity of carboxylic acids.[20]

In summary, we have achieved the oxidative coupling reaction of aldehydes with *N*,*N*′-disubstituted carbodiimides catalyzed by NHC under aerobic conditions. This reaction gives the corresponding *N*-acylurea derivatives in good to high yields. Various kinds of aldehydes including aliphatic ones and carbodiimides are applicable to this reaction.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) (a) Kim, S. M.; Kim, Y. S.; Yang, J. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 2529–2530. (b) Kang, S.; Joo, C.; Kim, S. M.; Han, H.; Yang, J. W. *Tetrahedron Lett.* **2011**, *52*, 502–504. (c) Yoshida, M.; Katagiri, Y.; Zhu, W.-B.; Shishido, K. *Org. Biomol. Chem.* **2009**, *7*, 4062–4066.

(17) (a) Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett.* **2006**, *8*, 1521–1524. (b) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665–667.

(18) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1974**, *96*, 5272–5274.

(19) (a) Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914–8915. (b) Sundén, H.; Engqvist, M.; Casas, J.; Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6532–6535. (c) Sarma, A. D.; Tipton, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 11252–11253.

(20) When the optimized reaction of **1a** and **2a** was carried out in the presence of 100 mol % of garvinoxyl free radical, the product **3aa** was obtained in 24% yield after 18 h. This result indicated that a radical pathway could be involved especially in the oxidation step with O_2.

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