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Amidations Using *N,N′*-Carbonyldiimidazole: Remarkable Rate Enhancement by Carbon Dioxide

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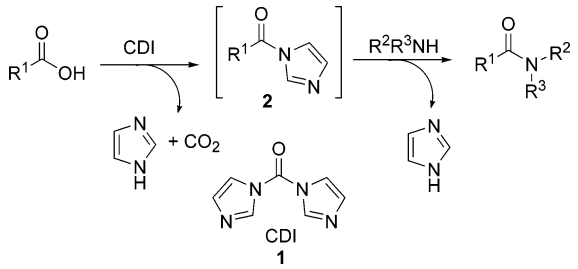
Abstract: Carbon dioxide catalyzes the reaction of imidazolides with amines to form amides. A substantial rate enhancement is observed in the presence of CO_2 compared to the CO_2-free case. The scope and limitations of this reaction are discussed.

N,N′-Carbonyldiimidazole (CDI, **1**) is a widely used reagent to form amides from carboxylic acids and amines (Scheme 1).[1] Typically, this is a one-pot procedure wherein a mixture of the acid and CDI is allowed to stir until the activation reaction to form the intermediate imidazolide **2** is complete. The amine is then added to the reaction mixture to lead to the desired amide. The method has been applied to a variety of aliphatic, aromatic, and heterocyclic carboxylic acids. The intermediate imidazolides **2** obtained upon reaction of carboxylic acids with CDI possess reactivity comparable to acid chlorides; however, they are more easily handled, and may be isolated if necessary. Moreover, imidazole, the byproduct obtained when the imidazolide reacts with the amine, is easily removed from the reaction mixture by an acidic wash. These advantages, coupled with the relatively low cost of CDI, render this method an attractive alternative to the carbodiimide-based reagents such as DCC and EDC.

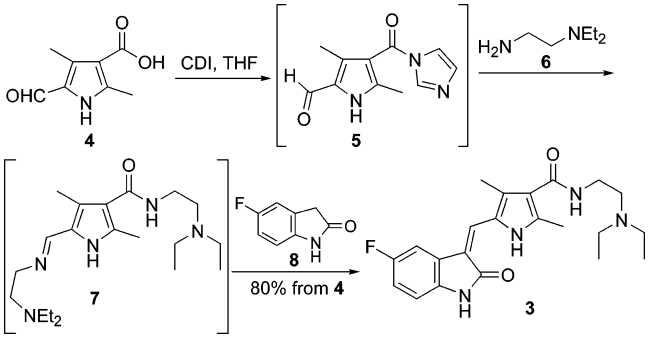
The synthesis of **3**, an exciting split kinase inhibitor under clinical development, is depicted in Scheme 2.[2] The key acid aldehyde **4** is activated with CDI to form the intermediate imidazolide **5** in situ. Addition of *N,N*-diethylethylenediamine (**6**) to the reaction mixture leads to the imine-amide intermediate, **7**. Imine formation competes with amide formation, necessitating the use of excess amine; however, the imine itself does not pose any problems in the subsequent coupling step. Coupling of **7** with 5-fluorooxindole **8** leads to the final product, **3**.[3]

During our exploratory studies on this route in the laboratory, the amidation reaction reached 90% conversion in ca. 4 h and was typically complete in less than 12 h. However, when attempts were made to run this chemistry in the pilot plant on a multi-kilogram scale, the amidation reaction was substantially slower, requiring almost 50 h to reach completion.

SCHEME 1



SCHEME 2



One potential explanation was that the CO_2 released in the imidazolide formation step was not removed completely from the reactor in the pilot plant prior to addition of diamine **6** and that this lingering CO_2 reacted with the amine to form the carbamate salt, thus slowing down the amidation reaction. To verify this hypothesis, two experiments were set up in the laboratory, starting with isolated imidazolide **5**. In one case, CO_2 was bubbled into a slurry of imidazolide **5** and imidazole in THF for 15 min prior to the addition of the amine, and the other was run under CO_2-free conditions. The reaction with CO_2 reached 88% conversion in 4 h, while the CO_2-free reaction was substantially slower and was only 37% complete in the same time.[4] These experiments clearly

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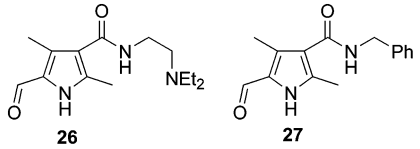
(2) (a) Tang, P. C.; Miller, T.; Li, X.; Sun, L.; Wei, C. C.; Shirazian, S.; Liang, C.; Vojkovsky, T.; Nematalla, A. S. WO 01/60814. (b) Mendel, D. B.; Laird, A. D.; Xin, X.; Louie, S. G.; Christensen, J. G.; Li, G.; Schreck, R. E.; Abrams, T. J.; Ngai, T. J.; Lee, L. B.; Murray, L. J.; Carver, J.; Chan, E.; Moss, K. G.; Haznedar, J. O.; Sukbuntherng, J.; Blake, R. A.; Sun, L.; Tang, C.; Miller, T.; Shirazian, S.; McMahon, G.; Cherrington, J. M. *Clin. Cancer Res.* **2003**, *9*, 327.

(3) (a) Jin, Q.; Mauragis, M. A.; May, P. D. PCT Int. Appl. WO 2003070725, 2003. (b) Guan, H.; Liang, C.; Sun, L.; Tang, P. C.; Wei, C. C.; Mauragis, M. A.; Vojkovsky, T.; Jin, Q.; Herrinton, P. M. PCT Int. Appl. WO 2002066463, 2002. (c) Mauragis, M. A.; Jin, A.; Fleck, T. J. Manuscript in preparation. (d) Manley, J. M.; Kalman, M. J.; Conway, B. G.; Ball, C. C.; Havens, J. L.; Vaidyanathan, R. *J. Org. Chem.* **2003**, *68*, 6447.

(4) The reactions were monitored by HPLC. Imines **7** and **9** were quantitatively hydrolyzed to the corresponding aldehydes, **26** and **27** respectively under the HPLC conditions.



26 27

10.1021/jo049949k CCC: $27.50
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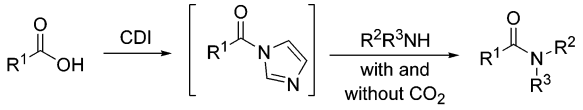
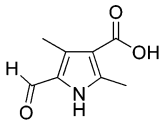
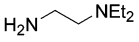
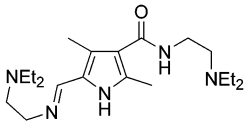
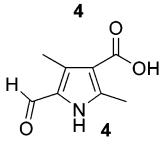
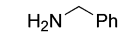
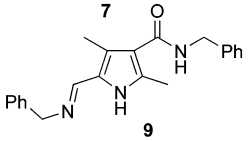
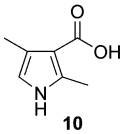
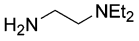
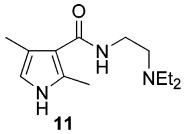
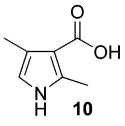
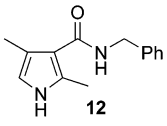
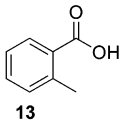
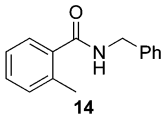
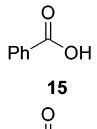
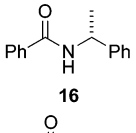
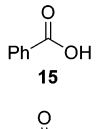
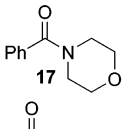
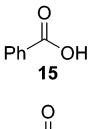
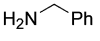
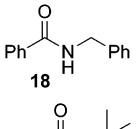
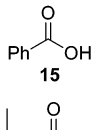
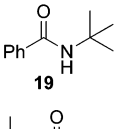
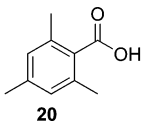
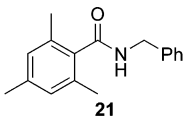
TABLE 1. Rates of Amidation of Imidazolides with and without CO_2



Entry	Acid	Amine	Product	$t_{1/2}$ (min)[a] With CO_2	$t_{1/2}$ (min)[a] CO_2-Free
1[b]	 **4**		 **7**	53	>330[c]
2[b]	 **4**		 **9**	101	217
3	 **10**		 **11**	98	410
4	 **10**		 **12**	161	>>510[d]
5	 **13**		 **14**	11	192
6	 **15**		 **16**	13	>275[e]
7	 **15**		 **17**	<15[f]	72
8	 **15**		 **18**	<1[g]	<10[h]
9	 **15**		 **19**	–	–
10	 **20**		 **21**	–	–

[a] $t_{1/2}$ is the time required for the amidation reaction to reach 50% conversion by HPLC. [b] The product imine−amides were hydrolyzed to the corresponding aldehyde−amides under the HPLC conditions. [c] The reaction was 48% complete in 330 min. [d] The reaction was 11% complete in 510 min. [e] The reaction was 43% complete in 275 min. [f] The reaction was 100% complete in 30 min. [g] The reaction was 97% complete in 1 min. [h] The reaction was 34% complete in 1 min and 92% complete in 10 min.

demonstrate that CO_2 has a beneficial rather than deleterious effect on the reaction rate! Based on these results, a conscious attempt was made to retain the CO_2 liberated in the first step in solution during the next pilot plant campaign. As expected, the amidation reaction reached ca. 90% conversion in 4 h and was complete in less than 12 h without any complications. In retrospect, better agitation and venting in the pilot plant in our first campaign led to removal of CO_2 from the reactor and thus slowed the amidation reaction.

In separate experiments, CO_2 was bubbled through solutions of the amine, imidazolide, and the solvent prior to the reaction. Another reaction was carried out at 50 psig CO_2. Interestingly, all these reactions proceeded at the same rate as the normal reaction (one-pot conversion of the acid to the amide via the imidazolide without

venting the CO_2). This suggests that only a critical amount of CO_2 in solution is needed to catalyze the reaction; more does not necessarily help.

Several substrates were examined in an attempt to explore the scope of this CO_2 catalysis, and the results are summarized in Table 1. We chose to use $t_{1/2}$ (time required for the amidation reaction to reach 50% completion) as a convenient point of comparison of the rates of the catalyzed and uncatalyzed reactions (see the Experimental Section for a typical procedure).

As seen in Table 1, the CO_2-catalyzed reactions were substantially faster than the corresponding CO_2-free reactions. Significantly, in the case of the reaction of the imidazolide of acid **10** with benzylamine, the CO_2-free reaction was only 11% complete after 8.5 h, while the catalyzed reaction reached 50% completion in less than 3 h (entry 4). Interestingly, the CO_2-catalyzed reactions in entries 5−7 reached completion within 30−60 min, while the CO_2-free reactions took several hours to reach even 50% conversion. In the case of the reaction of benzoyl imidazole with benzylamine, the catalyzed reaction was virtually complete within 1 min, while the uncatalyzed reached completion in ca. 10 min (entry 8). When either the amine or the acid was highly sterically encumbered, the reaction did not proceed at all (entries 9 and 10). The inference drawn from these experiments is that CO_2 catalyzes amidation of imidazolides; this effect is perceptible and pronounced when either the imidazolide or the amine is less reactive due to steric or electronic reasons (entries 1−7). In unhindered substrates, the effect still exists; but since the uncatalyzed reaction is inherently fast, the catalytic effect of CO_2 is barely noticeable. In cases where the sterics are overbearing (2,4,6-trimethylbenzoic acid or *tert*-butylamine), the reaction does not proceed at all.

The next question was: "can one 'jump-start' a slow, CO_2-free reaction by bubbling in CO_2 mid-way through the reaction?" The reaction of imidazolide **22** (derived from acid **10**) with benzylamine was chosen as the test reaction since the rate difference between the catalyzed and uncatalyzed reactions was most pronounced in this case (Table 1, entry 4). In the experiment, a mixture of **22**, imidazole and benzylamine was allowed to stir at 45 °C. After 1 h (ca. 1% conversion to the amide), CO_2 was sparged into the reaction mixture for 15 min, and the mixture was stirred at 45 °C. As expected, the reaction rate increased dramatically, and was nearly identical to that of the CO_2 catalyzed reaction (Figure 1). This conclusively establishes the fact that CO_2 catalyzes the reaction and may be used to "jump-start" slow amidation reactions.

In the case of the amidation reactions listed in Table 1, a precipitate was observed when CO_2 was bubbled through a solution of the amine in THF, suggesting the formation of the alkylammonium *N*-alkyl carbamate, **23**.[5] The ambident nucleophilic nature of these carbamates is well-documented. They have been shown to react with alkyl halides to give both *N*-alkylation[6] and *O*-alkylation products,[7] depending on the reaction conditions. In the course of their investigation on the reaction of amines with dimethyl carbonate (DMC) to form methyl carbamates, Aresta and co-workers established (through labeling studies) that the carbonyl carbon in the product was from DMC and not CO_2.[8] Their mechanistic studies suggested the intermediacy of carbamic−carbonic anhydride **24** (Scheme 3).

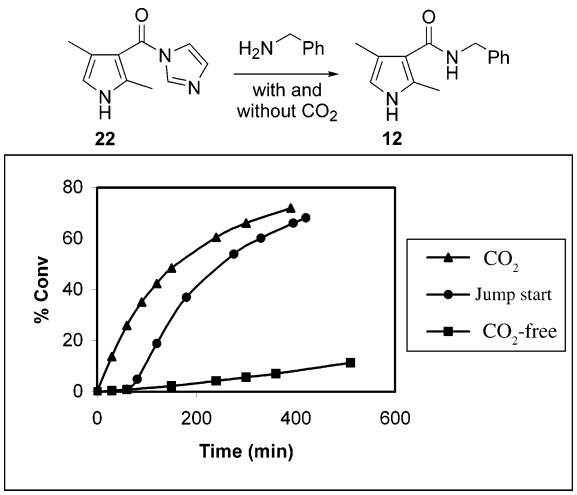
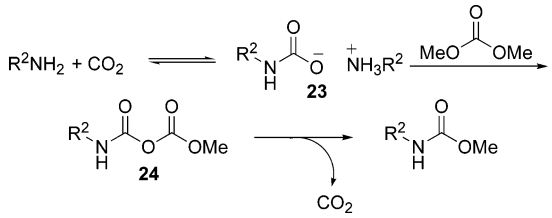


FIGURE 1. Rates of amidation with and without CO_2.

SCHEME 3

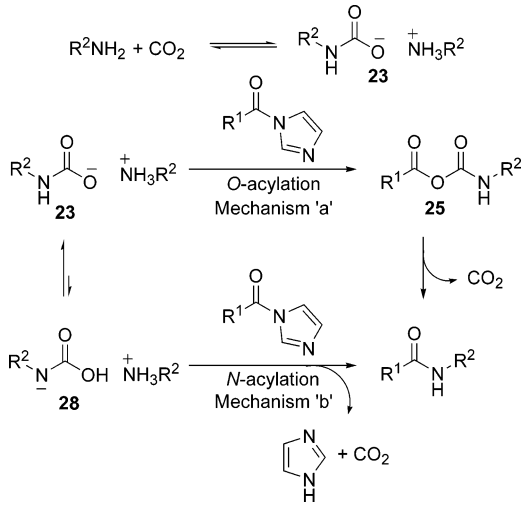


Based on our observations and literature precedent, the following mechanism may be postulated to explain the catalytic effect of CO_2 on amidation reactions. Reaction of the amine with CO_2 would lead to the alkylammonium *N*-alkyl carbamate, **23**. Nucleophilic attack of the oxygen center of carbamate **23** on the imidazolide would give intermediate **25** (analogous to **24**), which upon extrusion of CO_2 would lead to the amide (Scheme 4, mechanism a). Alternately, the nitrogen center of tautomer **28** may attack the carbonyl of the imidazolide to directly give the amide (Scheme 4, mechanism b).

In summary, we have demonstrated the catalytic effect of CO_2 in amidation reactions using CDI. This work clearly establishes the need to retain the CO_2 released in the imidazolide formation step in solution during the subsequent reaction of the imidazolide with the amine. While the mechanistic aspects of this reaction may require further elucidation, its utility in organic synthesis is clear.

(5) Hampe, E. M.; Rudkevich, D. M. *Chem. Commun.* **2002**, 1450.
(6) Yoshida, Y.; Ishii, S.; Watanabe, M.; Yamashita, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1534.
(7) (a) Aresta, M.; Quaranta, E. *Tetrahedron* **1992**, *48*, 1515. (b) Aresta, M.; Quaranta, E. *J. Org. Chem.* **1988**, *53*, 4154. (c) Aresta, M.; Quaranta, E. *J. Chem. Soc., Dalton Trans.* **1992**, 1893. (d) McGhee, W. D.; Pan, Y.; Riley, D. P. *J. Chem. Soc., Chem. Commun.* **1994**, 699. (e) McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B. *J. Org. Chem.* **1995**, *60*, 2820. (f) Salvatore, R. N.; Chu, F.; Nagle, A. S.; Kapxhiu, E.; Cross, R. M.; Jung, K. W. *Tetrahedron* **2002**, *58*, 3329.
(8) (a) Aresta, M.; Quaranta, E. *Tetrahedron* **1991**, *47*, 9489. (b) Aresta, M.; Dibenedetto, A. *Chem. Eur. J.* **2002**, *8*, 685.

SCHEME 4



Experimental Section

Typical Experimental Procedure. The following experimental procedures were used for the reactions depicted in Table 1. Authentic standards of all amides were synthesized by treatment of the corresponding acids and amines with EDC and HOBt, and the products were characterized by ^{1}H and ^{13}C NMR and compared to literature values.

Reactions Run in the Presence of CO_2. A mixture of the carboxylic acid (6 mmol) and CDI (7.2 mmol) in THF (20 mL) was stirred at 45 °C. When HPLC indicated complete conversion to the imidazolide, the mixture was concentrated to dryness in vacuo to remove all CO_2. This mixture containing the imidazolide and imidazole was diluted with 10 mL of THF. In a separate flask, CO_2 was bubbled through a solution of the amine (7.8 mmol, 1.3 equiv) in THF (10 mL) for 15 min. This solution was added to the solution of the imidazolide and imidazole and stirred at 45 °C. The progress of the reaction was monitored by HPLC. For the examples in entries 1 and 2 (Table 1), 3 equiv of amine was added for both the catalyzed and uncatalyzed reactions.

CO_2-Free Reactions. A mixture of the carboxylic acid (6 mmol) and CDI (7.2 mmol) in THF (20 mL) was stirred at 45 °C. When HPLC indicated complete conversion to the imidazolide, the mixture was concentrated to dryness in vacuo to remove all CO_2. This mixture containing the imidazolide and imidazole was diluted with 10 mL of THF. A solution of the amine (7.8 mmol, 1.3 equiv) in 10 mL of THF was added to the solution of the imidazolide and imidazole, and stirred at 45 °C. The progress of the reaction was monitored by HPLC. For the examples in entries 1 and 2 (Table 1), 3 equiv of amine was added for both the catalyzed and uncatalyzed reactions.

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Supporting Information Available: Characterization data for compounds **12** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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