

# Synthesis of Carbodiimides by I<sub>2</sub>/CHP-Mediated Cross-Coupling Reaction of Isocyanides with Amines under Metal-Free Conditions

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Supporting Information

ABSTRACT: An I<sub>2</sub>/CHP-mediated cross-coupling reaction of isocyanides with readily accessible amines via C-N formation is described for carbodiimide synthesis in moderate to excellent yields. This represents a metal-free strategy for a coupling reaction of isocyanides with amines, and R2-NH2 it provides an efficient approach for symmetric and unsymmetric functionalized carbodiimide derivative synthesis under mild conditions.

arbodiimides such as N,N'-dicyclohexylcarbodiimide (DCC) and N,N'-diisopropylcarbodiimide (DIC) are some of the most important chemical reagents in organic chemistry, and they have several useful applications including the synthesis of nucleotides, dehydration agents for peptide synthesis,<sup>2</sup> and intermediates or precursors for heterocycles.<sup>3–5</sup> In view of their high synthetic value, various methods have been developed for their preparation such as thermolysis-decarboxylation of isocyanates, dehydration of ureas, dehydrosulfurization of thioureas, and rearrangements of amidoximes.<sup>6</sup> However, these methods suffer from longer reaction time, toxic reagents, as well as poor atom economy. Palladium-catalyzed reactions of isocyanide insertion with amines provide an alternative strategy for the construction of N,N'-dialkylcarbodiimides with high atom economy.7 It is interesting to note that Au particles could also catalyze similar reactions in micromolar scales.<sup>8</sup> However, these methods have the drawbacks of limited substrates, low reaction scales, and expensive catalysts, which limit their further applications. Therefore, the development of an efficient protocol to construct carbodiimides under metal-free and mild conditions is more desirable.

More recently, we have reported a Co-catalyzed isocyanide insertion reaction with 2-arylanilines under O2 atmosphere for the creation of 6-aminophenanthridine derivatives. Inspired by this previous work and in continuation of our work on isocyanide-based reactions, we herein report an I<sub>2</sub>/CHPmediated cross-coupling reaction of isocyanides with readily accessible amines via C-N formation to construct various carbodiimides in moderate to excellent yields (Scheme 1).

Our investigations began with the reaction of methyl 3-(2aminophenyl)acrylate 1a and tert-butyl isocyanide 2a under different cobalt-catalyzed conditions. However, the reaction was messy, and no expected product was detected. To our surprise, carbodiimide 3aa was formed in 12% GC yield instead of indole derivative product by the reaction 1a and 2a in the presence of 5 mol % of I2 and 1 equiv of TBHP in 1,4-dioxane (Table 1, entry 4). Only trace amounts of 3a were detected in the absence of catalyst or oxidant (Table 1, entries 1 and 8). Increasing the amount of I2 to 20 mol % gave 3aa in 42% GC yield (Table 1,

Scheme 1. Oxidative Reactions of Amine with Isocyanide

a) Our previous work

entry 6). Other iodo-source catalysts such as TBAI, and NIS led to 3aa in poor yields (Table 1, entries 2 and 3). Further screening of different oxidants, such as TBPB, DTBP, O2, K2S2O8, and CHP, showed that CHP was the best oxidant (Table 1, entries 9-13). Increasing the amount of CHP to 2 equiv furnished 3aa in 69% GC yield (Table 1, entry 13). It should be noted that further reducing or increasing the amount of CHP resulted in a decrease in the yield of 3aa. When the reaction was carried out in toluene, DMF, DCE, DME, and THF, respectively, 3aa was observed in less than 46% GC yield in all cases (Table 1, entries 17–22). To our delight, the reaction in MTBE led to 3aa in 77% GC yield (Table 1, entry 23). Further examination of the reaction temperature (Table 1, entries 24 and 25) showed 3aa could be obtained in 81% GC yield (76% isolated yield) under reflux conditions (Table 1, entry 25). Therefore, the optimum reaction conditions feature 20 mol % of I2 and 2 equiv of CHP as the oxidant in MTBE at 55 °C for 3 h (Table 1, entry 25, 81% for 3aa).

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Table 1. Optimization of Reaction of Methyl 3-(2-Aminophenyl)acrylate 1a and *tert*-Butyl Isocyanide 2a<sup>a</sup>

entry	catalyst (mol %)	oxidant (equiv)	solvent	$yield^{b}$ (%)
1		$TBHP^{e}(1)$	1,4-dioxane	trace
2	$TBAI^{c}$ (20)	TBHP (1)	1,4-dioxane	trace
3	$NIS^d(20)$	TBHP (1)	1,4-dioxane	11
4	$I_{2}(5)$	TBHP (1)	1,4-dioxane	12
5	I <sub>2</sub> (10)	TBHP (1)	1,4-dioxane	26
6	I <sub>2</sub> (20)	TBHP(1)	1,4-dioxane	42
7	I <sub>2</sub> (30)	TBHP (1)	1,4-dioxane	41
8	I <sub>2</sub> (20)	Ar	1,4-dioxane	trace
9	I <sub>2</sub> (20)	$TBPB^{f}(1)$	1,4-dioxane	46
10	I <sub>2</sub> (20)	$DTBP^{g}(1)$	1,4-dioxane	trace
11	I <sub>2</sub> (20)	$O_2$	1,4-dioxane	trace
12	I <sub>2</sub> (20)	$K_2S_2O_8(1)$	1,4-dioxane	trace
13	I <sub>2</sub> (20)	$CHP^{h}(1)$	1,4-dioxane	53
14	I <sub>2</sub> (20)	CHP (0.5)	1,4-dioxane	18
15	I <sub>2</sub> (20)	CHP (2)	1,4-dioxane	69
16	I <sub>2</sub> (20)	CHP (3)	1,4-dioxane	22
17	I <sub>2</sub> (20)	CHP (2)	toluene	trace
18	I <sub>2</sub> (20)	CHP (2)	$\mathrm{DMF}^i$	trace
19	I <sub>2</sub> (20)	CHP (2)	MeCN	20
20	I <sub>2</sub> (20)	CHP (2)	$DCE^{j}$	22
21	I <sub>2</sub> (20)	CHP (2)	$DME^k$	46
22	I <sub>2</sub> (20)	CHP (2)	$THF^l$	26
23	I <sub>2</sub> (20)	CHP (2)	$MTBE^{m}$	77
24 <sup>n</sup>	I <sub>2</sub> (20)	CHP (2)	MTBE	22
25°	I <sub>2</sub> (20)	CHP (2)	MTBE	81
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"Reaction conditions: methyl 3-(2-aminophenyl)acrylate **1a** (0.5 mmol) tert-butyl isonitrile **2a** (1.2 equiv, 0.6 mmol), catalyst, and oxidant in 3 mL of solvent at 110 °C for 3 h. <sup>b</sup>Yields were determined by GC analysis with biphenyl as the internal standard. <sup>c</sup>TBAI = tertabutylammonium iodide. <sup>d</sup>NIS = N-iodosuccinimide. <sup>e</sup>70% TBHP solution in water, TBHP = tert-butyl hydroperoxide. <sup>f</sup>TBPB = tert-butyl peroxybenzoate. <sup>g</sup>DTBP = 2-(tert-butylperoxy)-2-methylpropane. <sup>h</sup>CHP = cumene hydroperoxide. <sup>i</sup>DMF = N,N-dimethylformamide. <sup>j</sup>DCE = 1,2-dichloroethane. <sup>k</sup>DME = ethylene glycol dimethyl ether. <sup>l</sup>THF = terahydrofuran. <sup>m</sup>MTBE = methyl tert-butyl ether. <sup>n</sup>The system was carried out at 55 °C.

To explore the scope and limitations of this approach, various anilines la-r were applied to the reaction with tert-butyl isocyanide 2a under the optimized metal-free conditions, and the results are summarized in Scheme 2. Most of the reactions proceeded smoothly to afford the desired carbodiimide products in moderate to excellent yields. The reaction of aniline 1b with 2a afforded the desired product 3ba in 70% yield. Anilines 1c-e with an o-, m-, or p-methyl group could be converted to the corresponding carbodiimides 3ca-ea in moderate yields (41-49%). Typically, functional groups including electron-donating tert-butyl, OMe, OEt, OBn (1f-i) and electron-withdrawing groups such as CN, COOEt, NO2, 1q, 1p, 1r were tolerated under identical conditions. However, anilines bearing electronwithdrawing groups showed less reactivity, and the reaction time should be extended to 24 h. When halogen-substituted anilines 1j-o were subjected to the reactions, the desired carbodiimides 3ja-oa were observed in good yields (65%-84%). It is worth noting that more bulky substrates 1e, 1l, and 1o could also undergo the transformation to furnish the desired products 3ea,

Scheme 2. Scope of Anilines 1a-s<sup>a,b</sup>

<sup>a</sup>Reaction condition: anilines 1a-r (0.5 mmol), tert-butyl isonitrile 2a (1.2 equiv, 0.6 mmol),  $I_2$  (20 mol %), and CHP (2 equiv) in 3 mL of MTBE at 55 °C. <sup>b</sup>Isolated yields.

**3la**, and **3oa** in 41%, 84%, and 65% yields, respectively. Unfortunately, the reaction of pyridin-2-amine **1s** could only give the corresponding product **3sa** in trace yield.

Next, we investigated the scope of isocyanides (Scheme 3). The reaction of 4-aminobenzonitrile 1q with adamantanyl isocyanide 2b performed well under the optimal conditions and led to the desired product 3qb in 72% yield. When the functional isocyanide 2c was used, we could also obtain the carbodiimide 2qc in 53% yield. When more bulky aryl

Scheme 3. Scope of Isocyanides 2b-d with 4-Aminobenzonitrile 1q

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isocyanides **2d**,e were subjected to the reactions, the reactions could also furnish carbodiimide derivatives **3qc**,**qd** in 21% and 42% yields, respectively.

The reaction is extendable to construct some useful carbodiimides such as DCC and DIC by the reaction of aliphatic amines with aliphatic isocyanides under the optimal conditions. The reaction of cyclohexanamine 1t with cyclohexyl isocyanide 2e proceeded well to furnish symmetric carodiimide DCC 3te in 51% GC yield (Scheme 4, eq 1). Similarly, DIC 3uf could also be

Scheme 4. Select Carbodiimides Synthesis by the Reaction of Isocyanides with Amines

obtained in 55% GC yield by the reaction of propan-2-amine 1u with isopropyl isocyanide 2f (Scheme 4, eq 2). Carbodiimide 3ra could also be generated in 90% yield by the reaction of 1v with 2g (Scheme 4, eq 3). This result indicated that the unsymmetric carbodiimide could be prepared by two different sets of the corresponding amine and isocyanide.

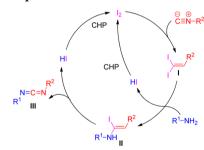
To further demonstrate the utility of our above reactions, we applied the carbodiimides in other transformations (Scheme 5). For example, the reaction of N-((tert-butylimino)methylene)aniline 3ba with piperidine in the presence of a catalytic amount of Yb(OTf)<sub>3</sub> easily led to the trisubstituted guanidine 4 in 95% GC yield (Scheme 5, eq 4). 10 When 3ba was treated with water, urea 5 could be formed in 72% GC yield (Scheme 5, eq 5). 11 Our protocol has also been successfully applied in the total synthesis of 1-(3-(4-fluorophenyl)-3,4-dihydro-2-(1H-imidazol-1-yl)-quinazolin-4-yl)propan-2-one 6, which shows good to significant fungicidal activity against Penicillium digitatum and strong binding interaction with the cytochrome P450-dependent sterol  $14\alpha$ -demethylase (CYP51). <sup>12</sup> I<sub>2</sub>/CHP mediated cross-coupling reaction of isocyanide 2h insertion reaction with amine 1a' gave carbodiimide 3a'n in 70% yield. Following the reaction of 3a'h with imidazole in the presence of K<sub>2</sub>CO<sub>3</sub> furnished 6 in 61% yield (Scheme 6). Compound 6 could be easily prepared over two steps based on our method instead of 5 steps as reported in the literature.

On the basis of the above results, a plausible reaction mechanism is proposed in Scheme 6. The reaction of isocyanide with iodine via 1,1-addition affords intermediate I. <sup>13</sup> Compound I reacts with amine to give intermediate II by dehydrohalogenation. Following the subsequent second time dehydrohalogenation, carbodiimide III is formed. Hydrogen iodide is oxidized by CHP to furnish iodine and complete the catalytic cycle.

In conclusion, we have developed a novel  $I_2/CHP$ -mediated cross-coupling reaction of isocyanides with readily accessible amines via C-N bond formation, affording carbodiimides in moderate to excellent yields under metal-free conditions. This

Scheme 5. Transformations of Carbodiimides and Total Synthesis of Antifungal Activity Molecule 6

Scheme 6. Proposed Mechanism



work not only represents a metal-free strategy for cross-coupling of isocyanides with amines but also provides an efficient approach to symmetric and unsymmetric functionalized carbodiimides under mild conditions. Further studies to understand this isocyanide insertion mechanism and their other synthetic applications are ongoing in our laboratory.

# **■** ASSOCIATED CONTENT

# Supporting Information

Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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#### ■ ACKNOWLEDGMENTS

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### REFERENCES

- (1) (a) Khorana, H. G. Chem. Rev. 1953, 53, 145. (b) Kurzer, F.; Douraghi-Zadeh, K. Chem. Rev. 1967, 67, 107. (c) Williams, A.; Ibrahim, I. T. Chem. Rev. 1981, 81, 589. (d) Zeni, G.; Larock, R. C. Chem. Rev. 2006, 106, 4644. (e) El-Faham, A.; Albericio, F. Chem. Rev. 2011, 111, 6557.
- (2) (a) Mukumoto, K.; Nojima, T.; Takenaka, S. Nucleic Acids Symp. Ser. 2004, 48, 251. (b) Tian, G.-L.; Lu, Y.-J.; Novak, B. M. J. Am. Chem. Soc. 2004, 126, 4082. (c) Monagle, J. J. J. Org. Chem. 1962, 27, 3851. (d) Sheehan, J. C.; Hess, G. P. J. Am. Chem. Soc. 1955, 77, 1067. (e) Wendlberger, G. Houben-Weyl: Methoden der Organischen Chemie; Georg Thieme Verlag: Stuttgart, 1974; Vol. 15/2, p 101. (f) Podlech, J. In Houben-Weyl Methods of Organic Chemistry. Synthesis of Peptides and Peptidomimetics; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme-Verlag: Stuttgart, 2001; Vol. E22a, pp 517—533. (g) Pozo, C.; Keller, A. I.; Nagashima, T.; Curran, D. P. Org. Lett. 2007, 9, 4167. (h) Sureshbabu, V. V.; Lalithamba, H. S.; Narendra, N.; Hemantha, H. P. Org. Biomol. Chem. 2010, 8, 835. (i) Reagents for Glycoside, Nucleotide, and Peptide Synthesis; Crich, D., Ed.; Wiley: New York, 2005. (j) Tan, D.; Mottillo, C.; Katsenis, A. D.; Strukil, V.; Friscic, T. Angew. Chem., Int. Ed. 2014, 53, 9321.
- (3) For recent selected examples, see: (a) Zeng, F.-L.; Alper, H. Org. Lett. 2010, 12, 1188. (b) Roberts, B.; Liptrot, D.; Luker, T.; Stocks, M. J.; Barber, C.; Webb, N.; Dods, R.; Martin, B. Tetrahedron Lett. 2011, 52, 3793. (c) Yuan, G.-D.; Liu, H.-Q.; Gao, J.-L.; Yang, K.-J.; Niu, Q.-S.; Mao, H.; Wang, X.-X.; Lv, X. J. Org. Chem. 2014, 79, 1749. (d) Lv, X.; Bao, W.-L. J. Org. Chem. 2009, 74, 5618. (e) Wang, F.; Cai, S.-J.; Liao, Q.; Xi, C.-J. J. Org. Chem. 2011, 76, 3174. (f) Larksarp, C.; Alper, H. J. Org. Chem. 1998, 63, 6229.
- (4) (a) Qiu, G.; Liu, G.; Pu, S.; Wu, J. Chem. Commun. **2012**, 48, 2903. (b) Qiu, G.; Lu, Y.; Wu, J. Org. Biomol. Chem. **2013**, 11, 798. (c) Qiu, G.; He, Y.; Wu, J. Chem. Commun. **2012**, 48, 3836.
- (5) For recent selected examples, see: (a) Ding, M.-W.; Xu, Z.-F.; Wu, T.-J. Synth. Commun. 1999, 29, 1171. (b) Ding, M.-W.; Zeng, G.-P.; Wu, T.-J. Synth. Commun. 2000, 30, 1599. (c) Ding, M.-W.; Xu, Z.-F.; Liu, Z.-J.; Wu, T.-J. Synth. Commun. 2001, 31, 1053. (e) Ding, M.-W.; Xu, S.-Z.; Zhao, J.-F. J. Org. Chem. 2004, 69, 8366. (f) Zhao, J.-F.; Xie, C.; Xu, S.-Z.; Ding, M.-W.; Xiao, W.-J. Org. Biomol. Chem. 2006, 4, 130. (g) Liu, M.-G.; Hu, Y.-G.; Ding, M.-W. Tetrahedron 2008, 64, 9052. (h) He, P.; Wu, J.; Nie, Y.-B.; Ding, M.-W. Tetrahedron 2009, 65, 8563. (i) Li, W.-J.; Liu, S.; He, P.; Ding, M.-W. Tetrahedron 2010, 66, 8151. (j) Liu, H.; Wang, H.-Q.; Ding, M.-W.; Liu, Z.-J.; Xiao, W.-J. J. Fluorine Chem. 2006, 127, 1584. (k) Liu, J.-C.; He, H.-W.; Ren, Q.-Y.; Ding, M.-W. Helv. Chim. Acta 2006, 89, 1337. (1) Ding, M.-W.; Chen, Y.-F.; Huang, N.-Y. Eur. J. Org. Chem. 2004, 3872. (m) Huang, N.-Y.; Liang, Y.-J.; Ding, M.-W.; Fu, L.-W.; He, H.-W. Bioorg. Med. Chem. Lett. 2009, 19, 831. (n) Hua, Y.-G.; Wang, Y.; Du, S.-M.; Chen, X.-B.; Ding, M.-W. Bioorg. Med. Chem. Lett. 2010, 20, 6188.
- (6) (a) Schmittel, M.; Steffen, J.-P.; Rodriguez, D.; Engelen, B.; Neumann, E.; Cinar, M. E. J. Org. Chem. 2008, 73, 3005. (b) Alajarin, M.; Bonillo, B.; Ortin, M.-M.; Sanchez-Andrada, P.; Vidal, A. Org. Lett. 2006, 8, 5645. (c) Vicente, J.; Abad, J.-A.; Lopez-Serrano, J.; Jones, P. G. Organometallics 2004, 23, 4711. (d) Anderson, J. C.; Bou-Moreno, R. Tetrahedron 2010, 66, 9182. (e) Babcock, J. R.; Sita, L. R. J. Am. Chem. Soc. 1998, 120, 5585. (f) Koketsu, M.; Suzuki, N.; Ishihara, H. J. Org. Chem. 1999, 64, 6473. (g) Kim, S.; Yi, K.-Y. J. Org. Chem. 1986, 51, 2613. (h) Kim, S.; Yi, K.-Y. Tetrahedron Lett. 1985, 26, 1661. (i) Olimpieri, F.;

- Bellucci, M. C.; Volonterio, A.; Zanda, M. Eur. J. Org. Chem. 2009, 35, 6179. (j) Fujiwara, S.-I.; Matsuya, T.; Maeda, H.; Shin-Ike, T.; Kambe, N.; Sonoda, N. Synlett 1999, 1, 75. (k) Wiese, S.; Aguila, M. J. B.; Kogut, E.; Warren, T. H. Organometallics 2013, 32, 2300. (l) Ito, Y.; Nirao, T.; Saegusa, T. J. Org. Chem. 1975, 40, 2981. (m) Tucker, H. U. B.; Sayigh, A. A. R. J. Am. Chem. Soc. 1972, 94, 3484. (n) Dondoni, A.; Barbaro, G.; Battaglia, A. J. Org. Chem. 1977, 42, 3372. (o) Mindiola, D. J.; Hillhouse, G. L. Chem. Commun. 2002, 38, 1840.
- (7) (a) Pri-Bar, I.; Schwartz, J. Chem. Commun. 1997, 33, 327.
  (b) Vlaar, T.; Cioc, R. C.; Mampuys, P.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. Angew. Chem., Int. Ed. 2012, 51, 13058.
- (8) (a) Lazar, M.; Angelici, R. J. J. Am. Chem. Soc. 2006, 128, 10613.
  (b) Angelici, R. J.; Lazar, M. Inorg. Chem. 2008, 47, 9155.
- (9) Zhu, T.-H.; Wang, S.-Y.; Tao, Y.-Q.; Wei, T.-Q.; Ji, S.-J. Org. Lett. **2014**, 16, 1260.
- (10) (a) Du, Z.; Li, W.-B.; Zhu, X.-H.; Xu, F.; Shen, Q. J. Org. Chem. **2008**, 73, 8966. (b) Zhang, X.-M.; Wang, C.-Y.; Qian, C.-W.; Han, F.-B.; Xu, F.; Shen, Q. Tetrahedron **2011**, 67, 8790. (c) Li, Z.; Xue, M.-Q.; Yao, H.-S.; Sun, H.-M.; Zhang, Y.; Shen, Q. J. Organomet. Chem. **2012**, 713, 27.
- (11) Anderson, J. C.; Bou-Moreno, R. Tetrahedron 2010, 66, 9182.
- (12) Li, W.-J.; Li, Q.; Liu, D.-L.; Ding, M.-W. J. Agric. Food Chem. 2013, 61, 1419.
- (13) (a) Kuehle, E.; Anders, B.; Zucmach, G. Angew. Chem., Int. Ed. 1967, 6, 649. (b) Kaim, El. L.; Grimaud, L.; Patil, P. Org. Lett. 2011, 13, 1261. (c) Currie, K. S.; Tennant, G. J. Chem. Soc. Chem. Commum. 1995, 2295. (d) Yu, H.; Zhang, M.-S.; Sun, W.-L.; Li, Y.-Z.; Gao, R. Lett. Org. Chem. 2010, 7, 566. (e) Yu, H.; Li, Y.-Z.; Liu, Q.; Zhang, M.-S.; Sun, W.-L. Chin. Chem. Lett. 2012, 23, 130.