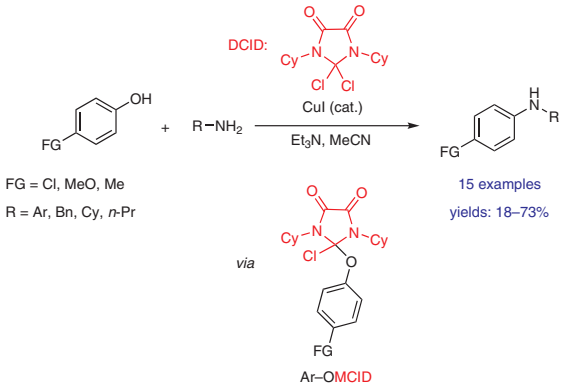
Synlett K. Madankar et al. Letter

A Novel Modified Cross-Coupling of Phenols and Amines Using Dichloroimidazolidinedione (DCID)

Kamelia Madankar
Javad Mokhtari*
Zohreh Mirjafary

Department of Chemistry, Science and Research Branch. Islamic Azad University, P.O. Box 14515/775, Tehran, Iran
j.mokhtari@srbiau.ac.ir

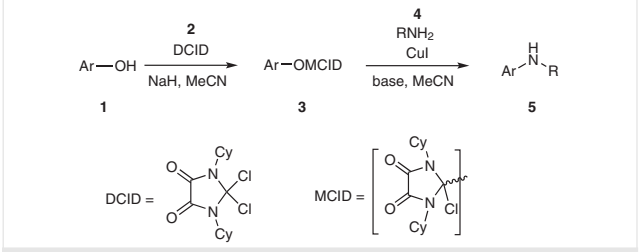


Received: 22.05.2020
Accepted after revision: 07.07.2020
Published online: 03.08.2020
DOI: 10.1055/s-0040-1707224; Art ID: st-2020-r0303-l

Abstract Phenols are considered as an ideal alternative to aryl halides as coupling partners in cross-coupling reactions. In the present work a copper-catalyzed cross-coupling of phenols with various aromatic and aliphatic amines for the synthesis of secondary aryl amines using dichloroimidazolidinedione (DCID) as a new and efficient activating agent has been developed. Substituted phenols were compatible with the standard reaction conditions. The two proposed mechanisms, which are based on the oxidation addition of copper with Ar-OMCID (MCID: Monochloroimidazolidinedione), are also discussed.

Key words cross-coupling, N-arylation, phenol, amines, dichloroimidazolidinedione, diarylamines

Carbon–nitrogen bonds are almost ubiquitously present in pharmaceuticals, agrochemicals, electronics, and dyes.[1] Given the importance of C–N bond formation, numerous efforts have been made to form this bond via transition-metal-catalyzed cross-coupling reactions since the 1970s.[2] Ullmann and Buchwald–Hartwig condensations are types of cross-coupling reactions which lead to formation of C–O, C–N and C–S bond catalyzed by copper and palladium.[3] In the early stages, aryl halides (iodide and bromide) were popular coupling partners because of their high reactivity. However, difficulties encountered in accessing aryl halides and the generation of toxic halogenated waste from the cross-coupling reaction limits their application in industry.[4] To this end, researchers were trying to find alternate cross-coupling counterparts with improved generality. Among these alternatives, phenol derivatives are good candidates because they are naturally abundant, readily available, non-toxic, and unique reaction intermediates in organic synthesis. Phenols have a C–O bond with high dissociation energy; therefore, it is necessary to transform phenols into activated phenol derivatives possessing rather weak C–O bonds such as aryl triflates, tosylates, mesylates, pivalates, and even ethers.[5–11] Therefore, in addition to the aforementioned, the development of new activated phenol derivatives for cross-coupling reactions has been needed. Herein, in continuation of our work on cross-coupling reactions,[12] in this paper we report a general, one-pot cross-coupling of phenols which are activated by dichloroimidazolidinedione (DCID) as a new and efficient reagent, with aromatic amines in the presence of catalytic amount of CuI (Scheme 1). Recently, DCID has been used in different organic syntheses including a Beckman's rearrangement of ketoximes,[13] chlorodehydroxylation of alcohols,[14] chemoselective amidation from carboxylic acids and amines,[15] multicomponent coupling of terminal alkynes,[16] halodehydrating agent,[17] and Suzuki–Miyaura cross-coupling[18] as a new reagent.



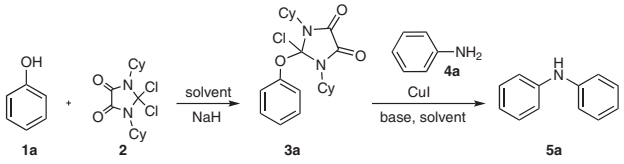
Scheme 1 One-pot cross-coupling of phenols and amines using DCID

DCID is readily available from the reaction of DCC with oxalyl chloride by known reported methods.[10] The chemical structure of the DCID was confirmed by elemental analysis and ^{1}H NMR and ^{13}C NMR spectra (see the Supporting Information). Firstly, to examine the role of DCID in the synthesis of diaryl amines, we used phenol and aniline to optimize the reaction conditions (Table 1). We found that reaction of phenol (1 eqiuv) and DCID (1 equiv) in MeCN and in the

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

presence of sodium hydride (1 equiv) as base led to Ph-OMCID **3a**. Upon addition of 1 equivalent of aniline and 20 mol% of CuI, diphenylamine was obtained in good yield.

Table 1 Optimization of the Reaction Conditions

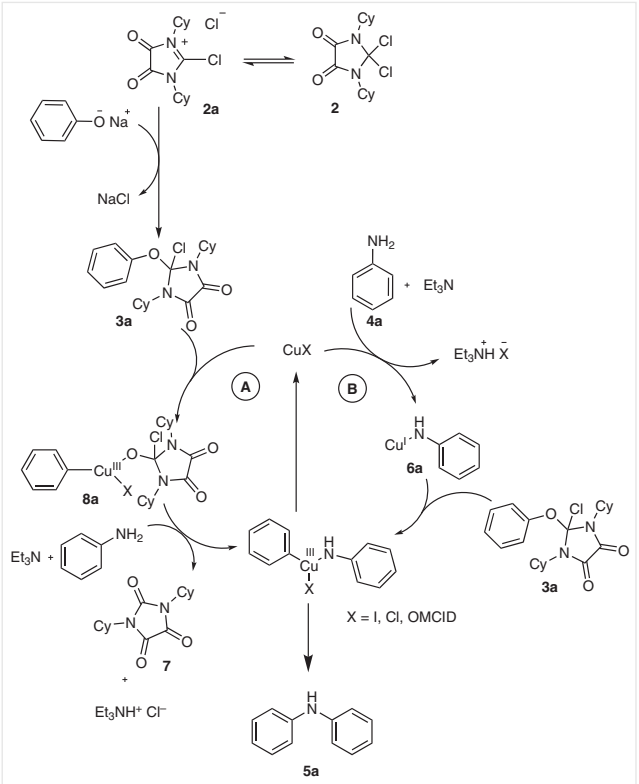


Entry	CuI (mol%)	Base	Solvent	Time (h)	Temp (°C)	Yield (%)
1	10	Et_3N	MeCN	24	80	30
2	20	Et_3N	MeCN	24	80	73
3	20	Et_3N	MeCN	18	80	65
4	20	Et_3N	MeCN	12	80	43
5	20	K_2CO_3	MeCN	24	80	56
6	20	Et_3N	THF	24	65	65
7	20	K_2CO_3	DMF	24	150	15
8	–	Et_3N	MeCN	24	80	–

[a] Reaction conditions: **1a** (1.0 mmol), **4a** (1.6 mmol), DCID (1.0 mmol), base (1.0 mmol) in MeCN (5 mL) at 80 °C.

Lower amounts of CuI (such as 10 mol%) led to decreased yields (Table 1, entry 1), therefore 20 mol% was chosen. On the other hand, when the reaction was done in DMF, the yield dropped sharply and formed only 5% of the product (entry 7). A control experiment for the investigation of the role of the catalyst was performed. In the absence of CuI, no conversion to the desired product could be observed (entry 8).

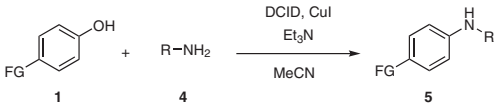
With the optimized reaction conditions in hand, the substrate scope was explored. As shown in Table 2, different aromatic and aliphatic amines reacted efficiently with phenol derivatives. Anilines with an electron-donating group in *para* position (Table 2, entries 5 and 6) furnished the products in good yields. An electron-withdrawing group such as 4-nitroaniline, however, led to 18% yield (entry 4), this may be due to the slow reaction of deactivated aniline with CuI and formation of copper(III) intermediate (Scheme 2). Also, 1-naphthyl amine and 2-aminopyrimidine (entries 7 and 8) reacted with phenol to yield the products **5g** and **5h** in good yields under identical conditions, respectively. On the other hand, aliphatic amines such as cyclohexyl amine, *n*-propyl amine, and benzylamine were also used in this reaction, generating the desired products with good yields (entries 9–11). Morpholine was also used to evaluate the reaction of the secondary amines in this reaction (entry 12) and compound **5l** was formed in 53% yield.



Scheme 2 Two possible pathways for the cross-coupling of phenol and amines using DCID

On the basis of the experimental facts and literature reports,[13,17] initially, the heterolytic cleavage of the C–Cl bond in DCID **1** occurs by the election donation of two amide nitrogen atoms adjacent to the quaternary carbon nucleus, affording 2-chloro-4,5-dioxo-imidazolinium chloride salt **2a**. Subsequently, the attack of phenoxide anion at C2 of **2a** forms the Ph-OMCID **3a**. The reaction then proceeds through two possible oxidative addition/reductive elimination mechanistic pathways[23] (Scheme 2). Cycle **B** is initiated by the reaction of aniline with CuI to generate species **6a**. Subsequently, oxidative addition of Ph-OMCID **3a** generates copper(III) intermediate, which undergoes further reductive elimination to give product **5a**. In cycle **A** the first step is an oxidative addition of the Ph-OMCID to copper to form a copper(III) intermediate. Afterwards, the MCID on copper is exchanged for the aniline and the obtained intermediate, via a reductive elimination step, releases the product **5a**, and the Cu(I) catalyst is regenerated. Additionally, it is noteworthy that species **7** was isolated and characterized by ^{13}C NMR and MS analysis (Figures S21 and S22 in the Supporting Information). These experimental results suggest that, under our reaction conditions, DCID-activated phenols and the resulting Ar-OMCIDs undergo an oxidative addition reaction.

Table 2 Cross-Coupling Reaction of Phenols with Different Amines Using DCID[a]



1 4 5

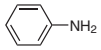
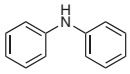
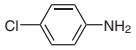
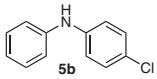
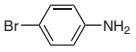
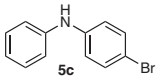
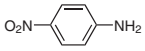
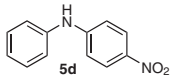
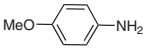
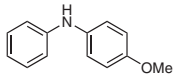
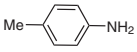
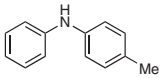
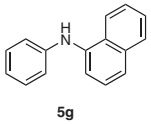
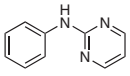
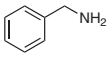
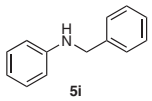
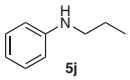
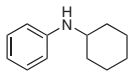
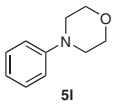
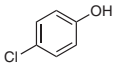
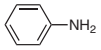
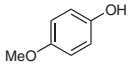
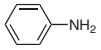
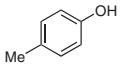
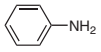
Entry	Phenol **1**	RNHR′ **4**	Product **5**	Yield (%)	Mp (°C)
1			 **5a**	73	52–53[12c]
2			 **5b**	74	72–74[12c]
3			 **5c**	68	86–89[12c]
4			 **5d**	18	134–135[12c]
5			 **5e**	61	100–102[19]
6			 **5f**	59	86–89[12c]
7			 **5g**	67	60–62[12c]
8			 **5h**	54	113–115[12c]
9			 **5i**	65	oil[20,b]
10			 **5j**	62	oil[20,b]
11			 **5k**	49	oil[21,b]
12			 **5l**	53	51–54[22]

Table 2 (continued)

Entry	Phenol **1**	RNHR′ **4**	Product **5**	Yield (%)	Mp (°C)
13			**5b**	62	72–74[12c]
14			**5e**	60	100-102[19]
15			**5f**	71	86–89[12c]

[a] Reaction conditions: **1** (1.0 mmol), **4** (1.6 mmol), DCID (1.0 mmol), CuI (20 mol%), Et_3N (1.0 mmol) in MeCN (5 mL) at 80 °C.
[b] Structures of compounds **5i**, **5j**, and **5k** were confirmed by NMR spectra (see Supporting Information).

In conclusion, we have developed a novel modified cross-coupling of phenols with various aromatic and aliphatic amines using dichloroimidazolidinedione (DCID) as a new and efficient reagent in the presence of copper(I).[24–27] Various substituted aromatic amines were obtained in good to excellent yields. The Ph-OMCID intermediate **3** is not isolated in this method and is therefore much more convenient and useful compared to the known reported methods. Investigations regarding the scope and application of this reagent (DCID) and further mechanistic studies are currently in progress.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707224.

References and Notes

(1) (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (c) Brown, B. R. *The Organic Chemistry of Aliphatic Nitrogen Compounds*; Cambridge University: Cambridge, **2004**. (d) McElroy, W. T.; DeShong, P. *Tetrahedron* **2006**, *62*, 6945. (e) Torres, J. C.; Pinto, A. C.; Garden, S. J. *Tetrahedron* **2004**, *60*, 9889. (f) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University: Cambridge, **2004**. (g) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443.
(2) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Ed.; Wiley-VCH: Weinheim, **1998**. (b) *Cross-Coupling Reactions. A Practical Guide*; Miaura, N., Ed.; Springer: Berlin, **2002**. (c) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Ed.; Wiley-VCH: Weinheim, **2004**.
(3) (a) Fanta, P. E. *Synthesis* **1974**, 9. (b) Castillo, P. R.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.
(4) (a) Rouhi, A. M. *Chem. Eng. News* **2004**, *82*, 49. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.
(5) (a) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85. (b) Ritter, K. *Synthesis* **1993**, 735.
(6) (a) Vorbrüggen, H. *Synthesis* **2008**, 1165. (b) Högermeier, J.; Reissig, H.-U. *Adv. Synth. Catal.* **2009**, *351*, 2747.
(7) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem. Eur. J.* **2011**, *17*, 1728.
(8) So, C. M.; Kwong, F. Y. *Chem. Soc. Rev.* **2011**, *40*, 4963.
(9) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081.
(10) Bisz, E.; Szostak, M. *ChemSusChem* **2017**, *10*, 3964.
(11) Tobisu, M.; Chatani, N. *Top. Curr. Chem.* **2016**, *374*, 41.
(12) (a) Panahi, L.; Naimi-Jamal, M. R.; Mokhtari, J.; Morsali, A. *Microporous and Mesoporous Materials* **2016**, *244*, 208. (b) Tahmasebi, S.; Khosravi, A.; Mokhtari, J.; Naimi-Jamal, M. R.; Panahi, L. *J. Organomet. Chem.* **2017**, *853*, 35. (c) Khosravi, A.; Tahmasebi, S.; Mokhtari, J.; Naimi-Jamal, M. R.; Panahi, L. *RSC Adv.* **2017**, *7*, 46022.
(13) Gao, Y.; Liu, J.; Li, Z.; Guo, T.; Xu, S.; Zhu, H.; Wei, F.; Chen, S.; Gebru, H.; Guo, K. *J. Org. Chem.* **2018**, *83*, 2040.
(14) Schilter, D.; Bielawski, C. W. *Org. Synth.* **2016**, *93*, 413.
(15) Li, J.; He, S.; Fu, H.; Chen, X.; Tang, M.; Zhang, D.; Wang, B. *Res. Chem. Intermed.* **2018**, *44*, 2289.
(16) Zhao, F.; Li, Y.; Wang, Y.; Zhang, W. X.; Xia, Z. *Org. Biomol. Chem.* **2014**, *12*, 3336.
(17) Moerdyk, J. P.; Bielawski, C. W. *Chem. Eur. J.* **2014**, *20*, 13487.
(18) Madankar, K.; Mokhtari, J.; Mirjafary, Z. *Appl. Organomet. Chem.* **2020**, e5383.
(19) Mallia, C. J.; Burton, P. M.; Smith, A. M. R.; Walter, G. C.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2016**, *12*, 1598.
(20) Xu, H.; Wolf, C. *Chem. Commun.* **2009**, 1715.
(21) Dang, T. T.; Shan, S. P.; Ramalingam, B.; Seayad, A. M. *RSC Adv.* **2015**, *5*, 42399.
(22) Lee, J.-C.; Wang, M.-G.; Hong, F.-E. *Eur. J. Inorg. Chem.* **2005**, *24*, 5011.
(23) Sperotto, E.; Klink, G. P. M.; Koten, G. V.; de Vries, J. G. *Dalton Trans.* **2010**, *39*, 10338.
(24) **Synthesis of Dichloroimidazolidinedione (DCID, 2)**
Compound **2** was synthesized by following Gao et al.,[13] with minor modifications. To *N*,*N*′-dicyclohexylcarbodiimine (DCC, 2 g, 1 mmol) in dry dichloromethane (25 mL) at 0 °C was added oxalyl chloride (0.9 mL, 1.05 mmol) dropwise. The reaction mixture was stirred for 1 h at room temperature. The solid material was separated by filtration and washed with cold dichloromethane. The recrystallization of white solid in ethanol yielded DCID (2,5 g, 97%); mp 174–176 °C. ^{1}HNMR (499.77 MHz, $CDCl_3$): δ = 3.97–4.00 (m, 2 H), 2.02–2.10 (m, 4 H, Cy), 1.73–1.87 (m, 4 H, Cy), 1.71–1.75 (m, 4 H, Cy), 1.66–1.69 (m, 2 H, Cy), 1.17–1.36 (m, 6 H, Cy) ppm.

(25) **Synthesis of 2-Chloro-1,3-dicyclohexyl-2-phenoxyimidazolidine-4,5-dione (3a)**

Typically, to an oven-dried 25 mL round-bottom flask containing dry MeCN was added phenol (0.047 g 0.5 mmol) and NaH (0.012 g, 0.5 mmol). The reaction mixture stirred for 30 min at room temperature, and then DCID (0.165 g, 0.5 mmol) was added. The reaction mixture was stirred for 1 h at room temperature and completion of the reaction monitored by TLC. After completion of the reaction salt was filtered, and the filtrate was evaporated under reduced pressure to yield a white solid (0.1 g, 96%).

Analytical Data of 2-Chloro-1,3-dicyclohexyl-2-phenoxyimidazolidine-4,5-dione (3a)

FTIR: ν = 2929, 2859, 1742, 1399, 1241, 1060 cm^{-1}. ^{1}HNMR (499.70 MHz, $CDCl_3$): δ = 7.16 (t, *J* = 7.44 Hz, 1 H), 6.82 (t, *J* = 8.14 Hz, 2 H), 6.76 (d, *J* = 7.59 Hz, 2 H), 3.95 (m, 1 H), 1.79 (m, 6 H), 1.71 (m, 4 H), 1.65 (m, 2 H), 1.18 (m, 4 H), 1.15 (m, 4 H) ppm. ^{13}CNMR (125.66 MHz, $CDCl_3$): δ = 156.7, 156.2, 128.9, 121.2, 116.3, 114.7, 31.8, 28.9, 28.7, 24.4 ppm. EI-MS: *m/z* = 393 [M^+ + 2], 356, 224, 181, 143, 99, 83, 56.

(26) **General Procedure for the One-Pot Cross-Coupling of Phenols and Amines Using DCID Catalyzed by CuI**

Typically for the synthesis of **5a**, to an oven-dried 25 mL round-bottom flask containing dry MeCN (5 mL) were added phenol (1 mmol) and NaH (0.024 g, 1 mmol). The reaction mixture stirred for 30 min at room temperature, and then DCID (0.330 g, 1 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, and completion of the reaction was monitored by TLC. After completion of the reaction, amines (1.6 mmol), Et_3N (0.101 g, 1 mmol), and CuI (0.038 g, 20 mol%) were added, and the reaction mixture was stirred at 80 °C for 24 h (TLC monitoring). For the purification of products, chromatography on silica gel was performed (EtOAc–heptane, 1:3). Structure of the diaryl amines was confirmed by comparison of melting point and NMR spectra reported in the literature (see Supporting Information).

Analytical Data of Diphenylamine (**5a**)

White solid; yield: 0.123 g, 73%; mp 52–53°C.[12c] ^{1}H NMR (499.70 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.2 Hz, 4 H), 7.52 (t, *J* = 6.9 Hz, 4 H), 7.48 (m, 2 H), 6.85 (s, 1 H, NH) ppm.

(27) **Scale-Up Synthesis of Diphenylamine (5a)**

To an oven-dried 250 mL round-bottom flask containing dry MeCN (50 mL) were added phenol (4.7 g, 50 mmol) and NaH (1.2 g, 50 mmol). The reaction mixture was stirred for 30 min at room temperature, and then DCID (16.5 g, 50 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, and completion of the reaction was monitored by TLC. After completion of the reaction aniline (7.23 mL, 80 mmol), Et_3N (6.97 mL, 50 mmol), and CuI (0.19 g, 20 mol%) were added, and the reaction mixture was stirred at 80 °C for 24 h (TLC monitoring). Purification of the product by chromatography on silica gel (EtOAc–heptane, 1:3) yielded compound **5a** (6.1 g, 72%).