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Palladium catalyzed synthesis of symmetrical and unsymmetrical ureas using chromium hexacarbonyl as a convenient and safe alternative carbonyl source

Mozhdeh Mozaffari,[a] and Najmeh Nowrouzi*[a]

Abstract: Pd-catalyzed synthesis of urea derivatives from aryl iodides and different aliphatic and aromatic amines using sodium azide and chromium hexacarbonyl is described. In this process, carbonylation of aryl iodides, curtius rearrangement of aroyl azides and nucleophilic addition of amines sequentially occurs to afford the products in good to excellent yields. This protocol is operationally simple and displays a broad substrates scope.

Introduction

Carbonylation process as a fundamental and promising transformation, is one of the most powerful methods for synthesizing both simple carbonyl compounds and more complex organic molecules. Urea is a very important class of carbonyl compounds from both theoretical and practical point of views because it is found in many compounds and materials. For example, its ability to hydrogen bind with biomolecular targets makes it a very practical scaffold in drug design.[1] Urea derivatives have a wide range of applications in pharmaceuticals, agricultural pesticides, antioxidants in gasoline and dyes for cellulose fibers.[2] They can also be used as efficient organocatalysts[3] or ligands for transition metals.[4] Recently Wrobel et al. discovered the nitroaryl urea derivatives with antiproliferative properties (Figure 1, **a**).[5] compound **b** is one of the multi target inhibitors with antiangiogenic and immunomodulator properties reported by Falomir et al. (Figure 1).[6]

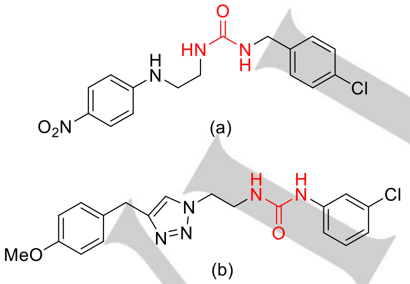

Figure 1. Two derivatives of urea with biological properties.

Due to the reasons given above, synthesis of ureas have been the subject of extensive experimental studies and many methodologies have been developed in the synthesis of these compounds including the reaction of amines with highly toxic phosgene,[7] stoichiometric reaction of amines and isocyanates,[8,9] palladium-catalyzed amidation,[10] oxidation of benzylic primary alcohols,[11] reaction of aromatic acids and amines in the presence of diphenylphosphorylazide,[12] and nitrogenation of aldehydes and acohols.[13] Carbonylation reaction is one of the most applicable protocol for this purpose. The commonly used carbonyl source for the synthesis of ureas is carbon monoxide,[14,15] which is highly toxic, flammable and realy hard to use. Therefore, in recent years, researchers have devoted their efforts to finding an efficient alternative for carbon monoxide. Some of the alternatives are include: carbon dioxide,[16,17] chloroform,[18] formic acid,[19] and methanol.[20]

Metal carbonyls are one of the best replacements for carbon monoxide. This solid carbonyl source is relatively stable and easy to handle, consequently, the use of them has been more developed recently in different carbonylation reactions.[21-23] herein, we decided to study the possibility of synthesizing symmetrical and unsymmetrical ureas through the curtius rearrangement using chromium hexacarbonyl as the carbonyl source. In this way, we used aryl iodide as the starting material, which is rarely reported by researchers. Recently, Wang et al. studied the Pd/C-catalyzed domino synthesis of urea derivatives from aryl iodides using chloroform,[18] and Wu et al. described a palladium-catalyzed domino procedure for the synthesis of unsymmetrical ureas in the presence of formic acid.[19] Arylation of phenylurea and urea using aryl halides have also been reported by Mane et al.[24], Kotecki et al.[10] and Artamkina et al.[25] In another study, Buchwald et al. reported a practical method for the synthesis of unsymmetrical ureas through a Palladium-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate[26] (Scheme 1).

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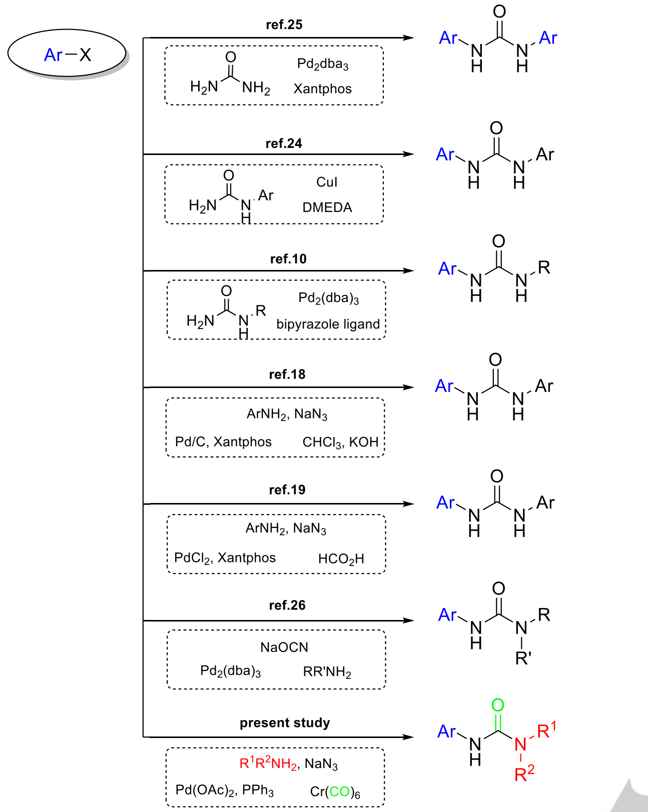
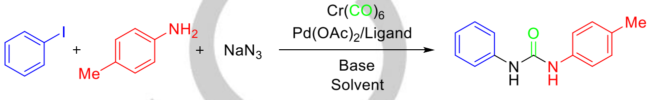


Scheme 1. Synthesis of ureas using aryl halides as starting material.

Results and Discussion

Initial study was started using iodobenzene (1.0 mmol) and 4-methylaniline (1.5 mmol) as model substrate in the presence of chromium hexacarbonyl (1.5 mmol), sodium azide (1.5 mmol), palladium acetate (5.0 mol%) and triphenylphosphine (10.0 mol%). The reaction was run in toluene at 100 °C and K_2CO_3 (2.0 mmol) was used as base. In this case, the desired product was obtained in 71% yield (Table 1, entry 1) and amide was formed as byproduct. Solvent screening showed that the coupling product could be obtained in H_2O and PEG-200, but in lower yield and no product could be detected when the reaction was carried out in DMF (Table 1, entries 2-4). Therefore, the subsequent reactions were performed in toluene. To study the effect of ligand on product formation, we first omitted triphenylphosphine from the reaction mixture. In this case, desired urea didn't produce efficiently (Table 1, entry 5). As shown in entries 6 and 7 of table 1, only trace amounts of product were obtained by using other ligands such as DMAP and TMEDA instead of Ph_3P. In order to check the role of base, a control experiment was performed and we found that in the absence of K_2CO_3, the reaction yielded the target product at low yield (Table 1, entry 8). Other bases such as Na_2CO_3, Bu_3N and KOH caused loss of efficiency (Table 1, entries 9-11). Due to the competition in nucleophilic addition between sodium azide and 4-methylaniline in the anion exchange step, the amount of these two starting materials should have an important effect on the yield. As expected, increasing the amount of sodium azide from 1.5 to 2.0 mmol, increased the yield (Table 1, entry 12). Similar improvement was observed using less amount of 4-methylaniline (Table 1, entry 13). After these improvements, we tried to decrease the catalyst loading. As shown in entry 14 of Table 1, decreasing the amount of palladium acetate to 1.0 mol% gave the product as well as 5.0 mol%, but further decrease, resulted the product in lower yield (Table 1, entry 15). Reducing the amount of triphenylphosphine from 10.0 mol% to 5.0 mol% and 3.0 mol%, did not have any significant effect on the conversion (Table 1, entries 16, 17).

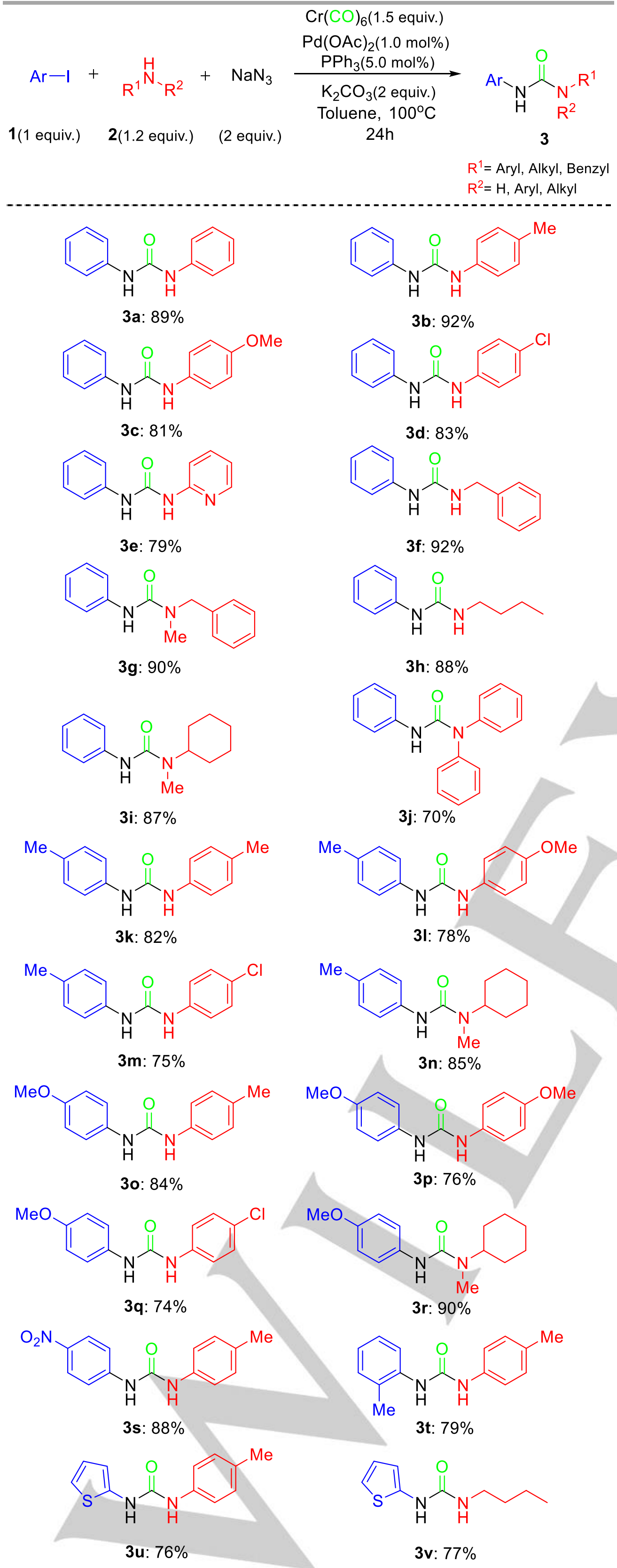
Table 1. Optimization of the reaction conditions[a].



Entry	Solvent/ 100 °C	Base	$Pd(OAc)_2$ (mol%)	Ligand	Yield[b] (Conversion value) (%)
1	Toluene	K_2CO_3	5	PPh_3	71(100)[c]
2	DMF	K_2CO_3	5	PPh_3	0 (0)
3	H_2O	K_2CO_3	5	PPh_3	35 (70)[c]
4	PEG-200	K_2CO_3	5	PPh_3	12 (25)[c]
5	Toluene	K_2CO_3	5	-	Trace (15)[c]
6	Toluene	K_2CO_3	5	DMAP	Trace (20)[c]
7	Toluene	K_2CO_3	5	TMEDA	Trace (20)[c]
8	Toluene	-	5	PPh_3	20 (25)
9	Toluene	Na_2CO_3	5	PPh_3	60 (80)[c]
10	Toluene	Bu_3N	5	PPh_3	46 (75)[c]
11	Toluene	KOH	5	PPh_3	52 (100)[d]
12[e]	Toluene	K_2CO_3	5	PPh_3	80 (100)[c]
13[f]	Toluene	K_2CO_3	5	PPh_3	92 (100)
14	Toluene	K_2CO_3	1	PPh_3	92 (100)
15	Toluene	K_2CO_3	0.5	PPh_3	67 (80)
16[g]	Toluene	K_2CO_3	1	PPh_3	91 (100)
17[h]	**Toluene**	**K_2CO_3**	**1**	**PPh_3**	**92 (100)**

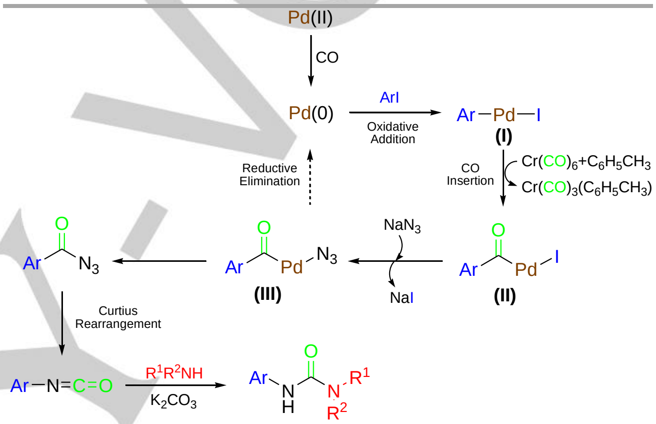
[a] General conditions: Iodobenzene (1.0 mmol), 4-methylaniline (1.5 mmol), sodium azide (1.5 mmol), base (2.0 mmol), $Pd(OAc)_2$ (5.0 mol%), ligand (10.0 mol%), $Cr(CO)_6$ (1.5 mmol), solvent (1.0 mL) , 100 °C, 24 h in a closed vessel.
[b] Yields are of pure isolated products.
[c] amide was formed as byproduct.
[d] several unwanted products were formed.
[e] Sodium azide (2.0 mmol)
[f] Sodium azide (2.0 mmol), 4-methylaniline (1.2 mmol)
[g] Sodium azide (2.0 mmol), 4-methylaniline (1.2 mmol), triphenylphosphine (5.0 mol%)
[h] Sodium azide (2.0 mmol), 4-methylaniline (1.2 mmol), triphenylphosphine (3.0 mol%)

After all these attempts to find the best reaction conditions, substrate scope was examined. At first, we investigated the reaction of various amines with iodobenzene. As it is shown in Scheme 2, all types of amines, including primary or secondary and aromatic or aliphatic amines tolerated this reaction and gave the desired product in high yield. Not only aromatic amines bearing electron-donating or electron-withdrawing substituents, but also hetero-aromatic amine easily react with other substrates, generating high yields (Scheme 2, 3e). In the case of diphenyl amine, a little decrease in the yield of product was observed, which might be due to the steric hindrance of phenyl groups (Scheme 2, 3j). To further extend the substrate scope, various amines were reacted with different aryl iodides. These reactions proceeded smoothly in accordance with the optimized reaction conditions, affording the corresponding products in excellent yields.



Scheme 2. Substrate scope of the reaction.

On the basis of the above experiments and our previous study on carbonylation reaction[23] and also according to the literatures review,[18,19] a proposed mechanism is shown in Scheme 3. Step 1 involves an oxidative addition in which Pd(0) inserts into the aryl iodide bond. Insertion of carbon monoxide (which in situ released from chromium hexacarbonyl[27]) gives intermediate (**II**). The reaction is followed by anion exchange with sodium azide to form intermediate (**III**). Reductive elimination of this intermediate smoothly occurs to produce aroyl azide along with the Pd(0) catalyst. Then, aroyl azide undergoes curtius rearrangement to generate aryl isocyanate, which, after the reaction with amine produces the corresponding urea.



Scheme 3. Proposed reaction mechanism.

Conclusions

In summary, we have developed a new protocol for the synthesis of different symmetrical and unsymmetrical ureas through the Pd-catalyzed carbonylation reaction using chromium hexacarbonyl as CO-source. This solid carbonyl source is one of the most applicable replacement for carbon monoxide which is a highly toxic gas with undesirable effects on human health and it's also difficult to apply in chemical procedures. So, different ureas are synthesized in good to excellent yields by a simple procedure under safe reaction condition. This protocol shows high functional-group tolerance on both starting materials. Due to the importance of carbonyl compounds in different branches of sciences, we are going to continue our studies on carbonylation reactions in order to reduce the use of toxic carbon monoxide for this purpose.

Acknowledgments

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Keywords: carbonylation • chromium hexacarbonyl • curtius rearrangement • palladium • urea

[1] A. D. Jagtap, N. B. Kondekar, A. A. Sadani, J. W. Chern, *Curr. Med. Chem*. **2017**, *24*, 622-651.

[2] a) I. Gallou, *Org. Prep. Proced. Int*. **2007**, *39*, 355-383; b) D. Bankston, J. Dumas, R. Natero, B. Riedl, M.-K. Monahan, R. Sibley, *Org. Process Res. Dev*. **2002**, *6*, 777-781; c) K. Matsuda, *Med. Res. Rev*. **1994**, *14*, 271-305.

[3] a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev*. **2007**, *107*, 5713-5743; b) T. J. Fisher, A. E. Mattson, *Org. Lett*. **2014**, *16*, 5316-5319.

[4] a) P. Gamez, B. Dunjic, M. Lemaire, *J. Org. Chem*. **1996**, *61*, 5196-5197; b) R. L. Lucas, M. K. Zart, J.M urkerjee, T. N. Sorrell, D. R. Powell, A. S. Borovik, *J. Am. Chem. Soc*. **2006**, *128*, 15476-15489; c) T. Yang, A. Ferrali, F. Sladojevich, L. Campbell, D.J. Dixon, *J. Am. Chem. Soc*. **2009**, *131*, 9140-9141.

[5] T. M. Wróbel, M. Kiełbus, A. A. Kaczor, V. Kryštof, Z. Karczmarzyk, W. Wysocki, A. Fruziński, S. K. Król, A. Grabarska, A. Stepulak, D. Matosiuk, *J. Enzyme Inhib. Med. Chem.* **2016**, *31*, 608-618.

[6] L. Conesa-Milián, E. Falomir, J. Murga, M. Carda, J. A. Marco, *Eur. J. Med. Chem*. **2019**, *15*, 87-98.

[7] a) J. S. Nowick, N. A. Powell, T. M. Nguyen, G. Noronha, *J. Org. Chem*. **1992**, *57*, 7364-7366; b) P. Majer, R. S. Randad, *J. Org. Chem*. **1994**, *59*, 1937-1938; c) R. A. Batey, V. Santhakumar, C. Yoshina-Ishii, S. D. Taylor, *Tetrahedron Lett*. **1998**, *39*, 6267-6270; d) Y. Patil-Sen, S. R. Dennison, T. J. Snape, *Bioorg. Med. Chem*. **2016**, *24*, 4241-4245; e) M. Blain, H. Yau, L. JeanG8rard, R. Auvergne, D. Benazet, P. R. Schreiner, S. Caillol, B. Andrioletti, *ChemSusChem* **2016**, *9*, 2269-2272; f) C. M. Sanabria, M. T. do Casal, R. B. A. de Souza, L. C. S. de Aguiar, M. C. S. de Mattos, *Synthesis* **2017**, *49*, 1648-1654; g) B. Lin, R. M. Waymouth, *J. Am. Chem. Soc*. **2017**, *139*, 1645-1652.

[8] a) M. J. Burk, J. G. Allen, *J. Org. Chem*. **1997**, *62*, 7054-7057; b) Y. Matsumura, T. Maki, Y. Satoh, *Tetrahedron Lett*. **1997**, *38*, 8879-8882; c) P. Gogoi, D. Konwar, *Tetrahedron Lett*. **2007**, *48*, 531-533.

[9] a) T. Curtius, J. Prakt. *Chem*. **1894**, *50*, 275-294; b) E. Wilhelm, R. Battino, *Chem. Rev*. **1973**, *73*, 1-9; c) E. F. V. Scriven, K. Turnbull, *Chem. Rev*. **1988**, *88*, 297-368.

[10] B. J. Kotecki, D. P. Fernando, A. R. Haight, K. A. Lukin, *Org. lett*. **2009**, *11*, 947-950.

[11] X. Q. Li, W. K. Wang, Y. X. Han, C. Zhang, *Adv. Synth. Catal*. **2010**, *352*, 2588-2598.

[12] A. R Kulkarni, S. Garai, G. A Thakur, *J. Org. Chem*. **2017**, *82*, 992-999.

[13] S. Song, P. Feng, M. Zou, N. Jiao, *Chin. J. Chem*. **2017**, *35*, 845-848.

[14] J. Zhao, Z. Li, S. Yan, S. Xu, M. A. Wang, B. Fu, Z. Zhang, *Org. lett*. **2016**, *18*, 1736-1739.

[15] B. Gabriele, G. Salerno, R. Mancuso, M. Costa, *J. Org. Chem*. **2004**, *69*, 4741-4750.

[16] a) M. Xu, A. R. Jupp, D. W. Stephan, *Angew. Chem. Int. Ed*. **2017**, *56*, 14277-14281; b) M. Xu, A. R. Jupp, M. Ong, K. Burton, S. Chitnis, D. W. Stephan, *Angew. Chem. Int. Ed*. **2019**, *58*, 5707-5711.

[17] F. Shi, Y. Deng, T. SiMa, J. Peng, Y. Gu, B. Qiao, *Angew. Chem. Int. Ed*. **2003**, *42*, 3257-3260.

[18] L. Wang, H. Wang, G. Li, S. Min, F. Xiang, S. Liua, W. Zheng, *Adv. Synth. Catal*. **2018**, *360*, 4585-4593.

[19] B. Chen, J. B. Peng, J. Ying, X. Qi, X. F. Wu, *Adv. Synth. Catal*. **2018**, *360*, 2820-2824.

[20] S. H. Kim, S. H. Hong, *Org. Lett*. **2016**, *18*, 2212-215.

[21] a) J. Wannberg, M. Larhed, *J. Org. Chem.* **2003**, *68*, 5750-5753; b) P. A. Enquist, P. Nilsson, M. Larhed, *Org. Lett*. **2003**, *5*, 4875-4878; c) P. A. Enquist, P. Nilsson, J. Edin, M. Larhed, *Tetrahedron Lett*. **2005**, *46*, 3335-3339; d) P. Caldirola, R. Chowdhury, A. M. Johansson, U. Hacksell, *Organometallics* **1995**, *14*, 3897-3900.

[22] a) L. Åkerbladh, L. R. Odell, M. Larhed, *Synlett* **2019**, *30*, 141-155; b) E. Etemadi-Davan, N. Iranpoor, P. Arshad, *Asian J. Org. Chem*. **2018**, *7*, 683-687; c) E. Etemadi-Davan, N. Iranpoor, *ChemistrySelect* **2016**, *1*, 4300-4304; d) N. Iranpoor, H. Firouzabadi, E. Etemadi-Davan, A. Nematollahi, H. R. Firouzi, *New J. Chem*. **2015**, *39*, 6445-6452.

[23] M. Mozaffari, N. Nowrouzi, M. Abbasi, *Appl. Organomet. Chem.* **2019**, *33*, 5049-5053.

[24] S. N. Gavade, R. S. Balaskar, M. S. Mane, P. N. Pabrekar, M. S. Shingare, D. V. Mane, *Chin. Chem. Lett*. **2011**, *22*, 675-678.

[25] G. A. Artamkina, A. G. Sergeev, I. P. Beletskaya, *Russ. J. Org*. **2002**, *38*, 538-545.

[26] E. V. Vinogradova, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 11132-11135.

[27] M. Kaushik, A. Singh, M. Kumar, *Eur. J. Chem*. **2012**, *3*, 367-394.

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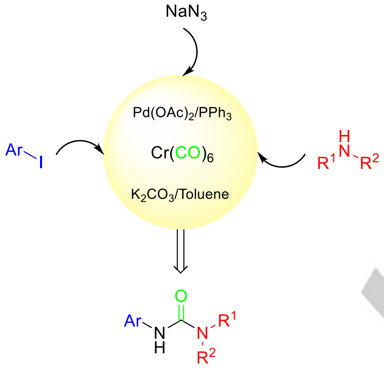
COMMUNICATION

Different symmetrical and unsymmetrical ureas are synthesized through a Pd-catalyzed carbonylation of aryl iodides using chromium hexacarbonyl. Curtius rearrangement occurs in the presence of sodium azide which is followed by nucleophilic addition of different amines to afford the products in good to excellent yields.



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Carbonylation, Synthesis of different ureas

*Mozhdeh Mozaffari, Najmeh Nowrouzi**

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