ORGANIC LETTERS

2013
Vol. 15, No. 4
948–951

Pd-Catalyzed Thiocarbonylation with Stoichiometric Carbon Monoxide: Scope and Applications

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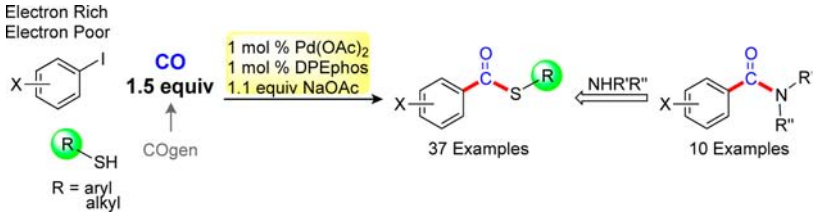
Received January 16, 2013

ABSTRACT



A general protocol for the Pd-catalyzed thiocarbonylation of aryl iodides with stoichiometric carbon monoxide has been established employing a catalytic system composed of $Pd(OAc)_2$ and DPEphos with low catalyst loading (1 mol %). Both electron-rich and -deficient aryl iodides proved effective for these couplings with aryl and alkyl thiols. The choice of the metal ligands and the solvent system was crucial for the efficiency and chemoselectivity of these transformations.

Thioesters are important structural entities widespread in biochemistry but which have also found extensive applications as activated esters for the synthesis of amides, esters, aldehydes, and ketones.[1] Protocols such as native chemical ligation invoking peptidyl thioesters have revolutionized synthetic approaches for accessing proteins.[2] Thioesters also have the advantage of being generally more stable than acyl halides, thereby simplifying purification and storage of these activated esters. Although procedures for the synthesis of thioesters from carboxylic acids or derivatives thereof are well-known, they nevertheless require the use of stoichiometric dehydration reagents.[3] Transition-metal-catalyzed carbonylation chemistry represents an alternative approach for the synthesis of unsaturated thioesters.

Carbonylation reactions promoted by Pd catalysis are now recognized as a key approach for the installment of carbonyl-containing functional groups.[4] Nevertheless, Pd-catalyzed thiocarbonylations of aryl halides are less well-known. Only two previous reports in the literature have demonstrated the feasibility of this transformation with aryl iodides. In 2008, Alper and co-workers reported the first Pd-catalyzed thiocarbonylation of aryl iodides using a phosphonium salt-based ionic liquid solvent in combination with 14 atm of CO pressure.[5,6] Later, Lei et al. in mechanistic studies on Pd-catalyzed carbonylation

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(3) (a) Zeiler, E.; Korotkov, V. S.; Lorenz-Baath, K.; Böttcher, T.; Sieber, S. A. *Bioorg. Med. Chem.* **2012**, *20*, 583. (b) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed.* **1978**, *17*, 522.

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(6) Alper's group has developed a number of other Pd-catalyzed thiocarbonylation reactions; see: (a) Xiao, W. J.; Alper, H. *J. Org. Chem.* **1997**, *62*, 3422. (b) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1998**, *63*, 2609. (c) Xiao, W. J.; Alper, H. *J. Org. Chem.* **1998**, *63*, 7939. (d) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1999**, *64*, 2080. (e) Xiao, W. J.; Alper, H. *J. Org. Chem.* **1999**, *64*, 9646. (f) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **2000**, *65*, 4138. (g) Xiao, W.-J.; Alper, H. *J. Org. Chem.* **2001**, *66*, 6229. (h) Xiao, W.-J.; Alper, H. *J. Org. Chem.* **2005**, *70*, 1802. (i) Cao, H.; Xiao, W.-J.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1807. (j) Li, C.-F.; Xiao, W.-J.; Alper, H. *J. Org. Chem.* **2008**, *74*, 888.

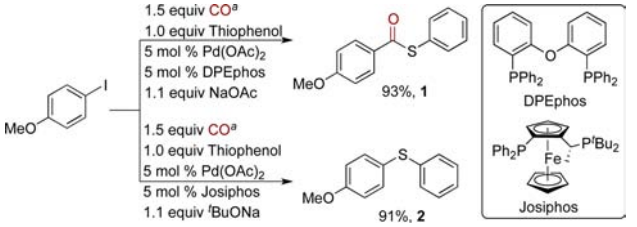
10.1021/ol400138m
Published on Web 02/05/2013

reactions demonstrated that the same transformation could be carried out using a sodium thiolate in a thiol/THF solvent mixture and a CO pressure of 10 atm.[7,8]

Recently, we reported a simple setup for running Pd-catalyzed alkoxy- and aminocarbonylations employing stoichiometric carbon monoxide generated from an acid chloride precursor.[9] This procedure provided a convenient access to amides without concerns about handling this toxic gas. The optimization of the catalytic system with low CO loadings was the key to success for such transformations. Furthermore, the method proved to be easily adaptable for ^{13}C- and ^{14}C-isotope labeling of pharmaceutically relevant small molecules.[10] In this paper, we demonstrate that through optimization of the catalytic system and the reaction conditions a diverse array of aromatic thioesters can be obtained from the reaction of thiols with both electron-rich and electron-deficient aryl iodides using a simple procedure with only stoichiometric amounts of carbon monoxide. The method also lends itself as an ideal technique for isotope labeling of the carbonyl group.

In order to identify effective conditions for promoting the Pd-thiocarbonylation, we initially relied on the catalytic system developed by Hartwig and co-workers in their efficient synthesis of aryl thioethers using the combination of $Pd(OAc)_2$/Josiphos (PhPF-*t*-Bu) as the catalytic system and sodium *tert*-butoxide as the base in DME.[11] All reactions were carried out applying a two-chamber system with the ex situ production of CO as earlier reported.[9] However, coupling of thiophenol with *p*-iodoanisole under these conditions gave the direct coupling product **2** in a 91% yield with only traces of the desired thioester **1** (Scheme 1). A ligand and base screening revealed that DPEphos in combination with sodium acetate as the base

Scheme 1. Results from Optimization Studies



[a] Ex situ generated CO from 9-methylfluorene-9-carbonyl chloride (COgen).

afforded a complete reversal in chemoselectivity leading to compound **1** in a gratifying yield of 93% (see the Supporting Information for the optimization table). A few other bidentate ligands also proved effective for this conversion including DPPF and Xantphos. However, the yields of thioester **1** were generally approximately 10−20% lower than for DPEphos. The catalytic loading could also be reduced from 5 to only 1 mol % without a significant deterioration in the thioester yield (89% isolated yield of **1**). Significantly, only 1.5 equivalents of carbon monoxide were necessary for this reaction to run effectively.

The generality of the reaction conditions was next tested on a variety of aryl iodides and thiols as illustrated in Scheme 2. Coupling of thiophenol to a number of differently functionalized aryl iodides provided the thioesters in good yields (**1**−**16**). Even heteroaromatic iodides proved effective for these carbonylative couplings as depicted with the indole and thiophene ring system leading to products **14/15** and **16**, respectively, in over 80% yield. With the former, partial deprotection of the indole nitrogen took place under the reaction conditions, but the combined thioester yield still attained 90%. A few other aromatic thiols were also successfully tested as represented by compounds **17**−**19**. Finally, three alkyl thiols were run, providing the functionalized esters (**20**−**22**) in approximately 70% yield. In particular, compounds **21** and **22** are generated from two cysteine derivatives. No epimerization was noted on the ^1H NMR spectra of compound **22** attesting to the mildness of the reaction conditions employing the weak base, sodium acetate. Applying the reaction conditions to electron-deficient aryl iodides proved to be somewhat problematic. In general, the thioethers were obtained as the major product. Increasing the number of equivalents of CO and, hence, the overall pressure of the reaction system, provided a partial solution, but not one which was satisfactory. This observation on the reactivity of such substrates corresponds well with a mechanism whereby the CO-insertion step into the Pd−aryl bond is slow compared to the other steps of the catalytic cycle.[12] A solvent screening was undertaken to investigate its effect on the chemoselectivity in

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(8) Recently, Oshima and co-workers showed the possibility of using the iron carbonyl complex $[CpFe(CO)_2]_2$ as a CO precursor for Pd-catalyzed thioarylation of a few simple aryl iodides in varying yields. Although the method also makes use of stoichiometric carbonylation, it nevertheless requires the presence of a toxic transition-metal carbonyl complex. Nakaya, R.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2011**, *40*, 904.

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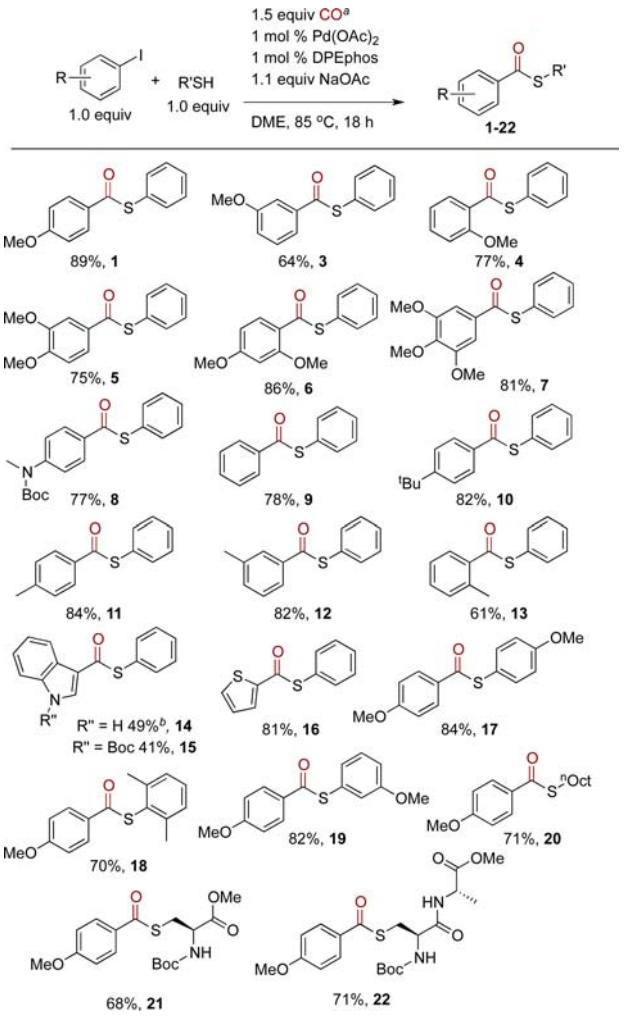
(12) In this case, the product yields obtained with the electron-deficient aryl halides are generally lower than those for the electron-rich substrates. For examples, see: Wu, X.-F.; Neumann, H.; Spannenberg, A.; Schulz, T.; Jiao, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 14596 and ref 10a,10f.

Scheme 2. Thiocarbonylation with Electron-Rich Aryl Iodides



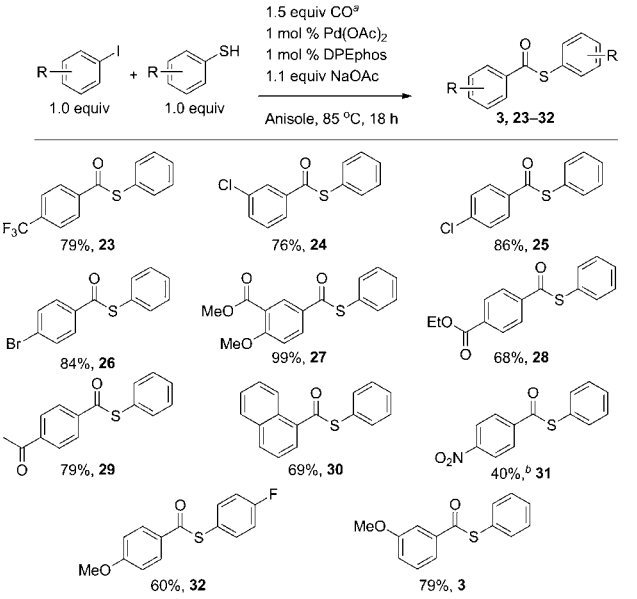
[a] Chamber 1: thiol (0.25 mmol), *p*-iodoanisole (0.25 mmol), $Pd(OAc)_2$ (2.5 μmol), DPEphos (2.5 μmol), NaOAc (0.28 mmol), DME (1.0 mL). Chamber 2: $Pd(dba)_2$ (13 μmol), P^tBu_3:HBF_4 (13 μmol), 9-methylfluorene-9-carbonyl chloride (0.38 mmol, 1.5 equiv), Cy_2NMe (0.56 mmol), DME (1.5 mL). [b] $Pd(OAc)_2$ (5.0 μmol) and DPEphos (5.0 μmol) were used in this reaction. Partial deprotection was observed.

the reaction of *p*-trifluoromethylphenyl iodide with thiophenol (see the Supporting Information). Of the several solvents tested (including toluene, proprionitrile, dioxane, CPME, and trifluorotoluene), the use of anisole furnished the thioester **23** in a good 79% yield (Scheme 3).

The scope of the thiocarbonylation procedure with the electron-poor aryl iodides is shown in Scheme 3. In most cases, good to excellent yields of the thioesters **23**–**32** were obtained. Even in the case of the *p*-nitro derivative, the desired compound **31** was formed.[13] Although the exact role of the solvent for promoting carbonylation is speculative, it is interesting to note that in the case of

(13) For these substrates, the corresponding thioethers were obtained as the byproduct arising from the direct coupling. Nevertheless, the separation by column chromatography proved to be facile due to the relatively large R_f difference between the two sulfur-containing products.

Scheme 3. Thiocarbonylation with Electron-Deficient Aryl Iodides



[a] Chamber 1: Thiophenol (0.25 mmol), iodide (0.25 mmol), $Pd(OAc)_2$ (2.5 μmol), DPEphos (2.5 μmol), NaOAc (0.28 mmol), anisole (1.0 mL). Chamber 2: $Pd(dba)_2$ (13 μmol), P^tBu_3 (13 μmol), 9-methylfluorene-9-carbonyl chloride (0.38 mmol, 1.5 equiv), Cy_2NMe (0.56 mmol), anisole (1.5 mL). [b] 3.0 equiv of CO was generated in chamber 2.

Pd-mediated carbonylative Suzuki reactions employing ligandless conditions anisole proved to be the only effective solvent for these transformations.[14]

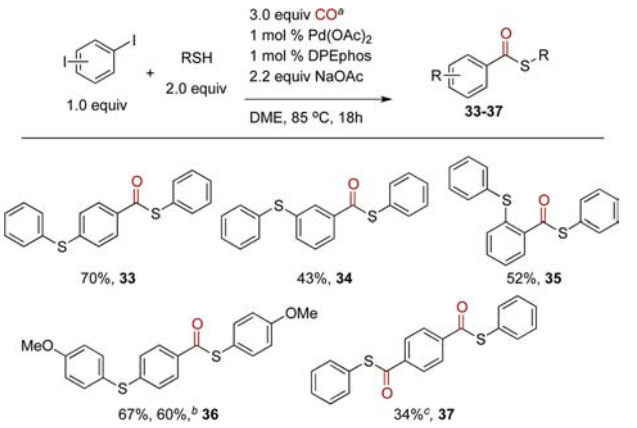
An interesting observation was made in the reaction of the three regioisomeric diiodobenzenes with either thiophenol or its *p*-methoxy derivative (Scheme 4). In all cases, the major products **33**–**36** resulted from a thiocarbonylation/thioarylation sequence even though 3 equiv of CO was applied. Although the reaction sequence order was not determined, it is worth noting that the double thioarylation product was obtained in better yields than the corresponding dithioester. It is interesting to note that a switch of DME to anisole as the solvent in the reaction with 1,4-diiodobenzene led to the formation of the dithioester **37** as the major product.

The value of the thioesters for amide library synthesis is illustrated with a few examples in Scheme 5. All amides (**38**–**45**) were prepared using simple coupling procedures from the thioester and are nonoptimized. They provide a good illustration of the diversity of compounds that can be obtained from a simple and easily storable thioester.[15]

(14) (a) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726. (b) Khedkar, M. V.; Tambade, P. J.; Qureshi, Z. S.; Bhanage, B. M. *Eur. J. Org. Chem.* **2010**, 6981 and references cited therein.

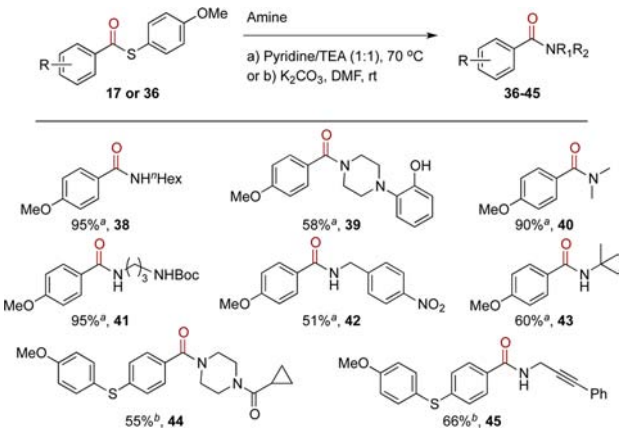
(15) The amide, *tert*-butyl (3-(4-((4-methoxyphenyl)thio)benzamido)-propyl)carbamate (**46**) (see the Supporting Information), was prepared via a one-pot procedure from 1,4-diiodobenzene, *p*-methoxythiophenol, and subsequent addition of *tert*-butyl (3-aminopropyl)carbamate under basic conditions. The desired product was isolated in 34% yield.

Scheme 4. Thiocarbonylation/Thioarylation with Diiodobenzene



[a] Chamber 1: thiol (0.50 mmol), iodide (0.25 mmol), $Pd(OAc)_2$ (2.5 μmol), DPEphos (2.5 μmol), NaOAc (0.55 mmol), DME (1.0 mL). Chamber 2: $Pd(dba)_2$ (25 μmol), P^tBu_3 (25 μmol), 9-methylfluorene-9-carbonyl chloride (0.76 mmol, 3.0 equiv), Cy_2NMe (1.13 mmol), DME (3.0 mL). [b] Reaction scaled up 5× (see the Supporting Information). [c] Anisole was used.

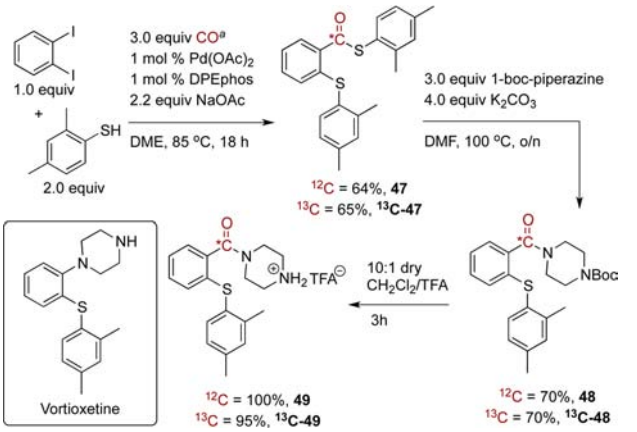
Scheme 5. Amide Formation from Thioesters **17** and **36**



[a] Thioester (0.37 mmol), amine nucleophile (0.55 mmol), triethylamine (0.5 mL), pyridine (0.5 mL). [b] Thioester (0.11 mmol), amine nucleophile (0.16 mmol), K_2CO_3 (0.21 mmol), DMF (1.0 mL).

Finally, we have exploited the thiocarbonylation/thioarylation protocol to prepare an interesting amide version of the new antidepressive agent, vortioxetine,[16] including its ^{13}C-isotope derivative (Scheme 6). The sequential transformation could be carried out with

Scheme 6. Synthesis and ^{13}C-Labeling of an Amide Analogue of Vortioxetine



[a] Chamber 2: $Pd(dba)_2$ (25 μmol), P^tBu_3 (25 μmol), 9-methylfluorene-9-carbonyl chloride (0.76 mmol, 3.0 equiv), Cy_2NMe (1.13 mmol), DME (3.0 mL).

o-diiodobenzene and 2,4-dimethylthiophenol with only 1.5 equiv of CO generated in the two-chamber system. This furnished a satisfactory 64% yield of **47** and a 65% yield of ^{13}C-**47** from ^{13}C-labeled CO. Subsequent amide formation with *N*-Boc pyrazine and acid-promoted deprotection led to a 70% isolated yield for both **49** and ^{13}C-**49**.

In conclusion, a catalytic system was developed for the Pd-catalyzed thiocarbonylation of aryl iodides with thiols exploiting a simple setup and reaction conditions, which use only stoichiometric carbon monoxide. Both electron-rich and electron-deficient aryl iodides could be applied and the nature of the metal ligands and the solvent system proved crucial for the chemoselectivity of these transformations. A protocol, which allows expansion of this chemistry to other aromatic halides, is currently under investigation and will be reported in due course.[17]

Acknowledgment. We are deeply appreciative of generous financial support from the Danish National Research Foundation, the Danish Natural Science Research Council, the Villum Foundation, the Carlsberg Foundation, the Lundbeck Foundation, and Aarhus University.

Supporting Information Available. Experimental details and copies of ^1H NMR and ^{13}C NMR spectra for all coupling products. This material is available free of charge via the Internet at http://pubs.acs.org

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(17) Preliminary investigations in the coupling of bromoanisole with thiophenol in anisole as the solvent applying the described catalytic system provided a 55% conversion to a mixture of the thioester and the thioether after a reaction time of 18 h and heating to 120 °C.

The authors declare no competing financial interest.