ChemComm

Accepted Manuscript

Volume 52 | Number 1 | 4 January 2016 | Pages 1–216

ChemComm

Chemical Communications
www.rsc.org/chemcomm

ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

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Reactivity differences of Sc₃N@C₂ₙ (2n = 68 and 80). Synthesis of the first methanofullerene derivatives of Sc₃N@C₂ₙ

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A one-pot route to thioamides discovered by gas-phase studies: palladium-mediated CO$_2$ extrusion followed by insertion of isothiocyanates

Asif Noor,[a] Jiawei Li,[a] George N. Khairallah,[a] Zhen Li,[a] Hossein Ghari,[b] Allan J. Canty,[c] Alireza Ariafard,*[b] Paul S. Donnelly*,[a] and Richard A. J. O'Hair*[a]

A new palladium mediated "one pot" synthesis of thioamides from aromatic carboxylic acids (ArCO$_2$H + RNCS → ArC(S)NHR + CO$_2$) was discovered by gas-phase experiments and theoretical studies. Palladium-mediated decarboxylation of aromatic carboxylic acids followed by addition of substituted isothiocyanates leads to the corresponding thioamide derivatives.

A desire to prepare new and known materials by efficient chemical synthesis using methods that are as environmentally benign as possible stimulates continued efforts to discover new reactions.[1-3] Computational chemistry is often used to probe the mechanisms of new reactions[4] and mass spectrometry (MS) is often used to characterise products but rarely have these techniques been used together as tools for the discovery of new reactions.[6] Here, we report their use to direct the hypothesis driven discovery of a new method to synthesise thioamides, an important class of compounds with applications in medicinal chemistry.[7]

The method involves 'swapping' the carboxylate functional group of readily available aromatic carboxylic acids (with the loss of CO$_2$) for a heterocumulene (eq. 1). This new method could prove to be an attractive alternative to conventional methods that require multiple steps and/or harsh reaction conditions.[8]

$$ArCO_2H + RNCS \rightarrow ArC(S)NHR + CO_2 \qquad (1)$$

Density Functional Theory (DFT) calculations suggested reactions represented by (1) to be exothermic for typical substrates,[9] and this led us to investigate palladium mediated decarboxylative transformation of aromatic carboxylic acids into thioamides (Scheme 1). Many of the individual steps of the reaction scheme have precedence but they have not been used together to achieve a 'one pot' synthesis of thioamides from carboxylic acids.[10-15]
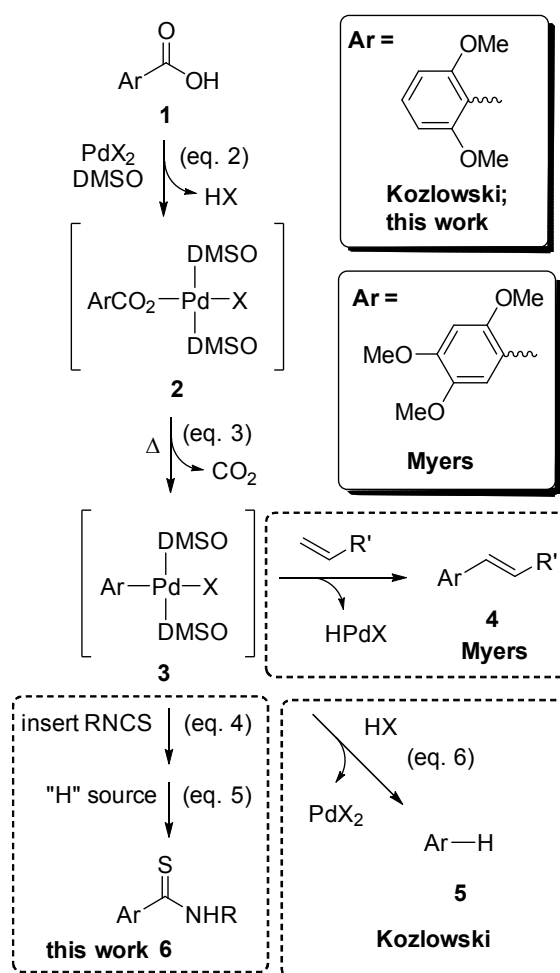
Scheme 1 Key reactions of relevance to palladium catalysed decarboxylative transformation of aromatic carboxylic acids into thioamides (eq. 1): The decarboxylative Heck reaction **1→2→3→4** (Myers);[12] protodecarboxylation **1→2→3→5** (Kozlowski);[13] and thioamide synthesis **1→2→3→6** (this work) share the same steps for the formation of the organopalladium intermediate (**3**), but differ in its subsequent reactions.

a. *School of Chemistry, University of Melbourne, Melbourne, Victoria 3010, Australia. E-mail: pauld@unimelb.edu.au; rohair@unimelb.edu.auddress*
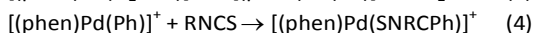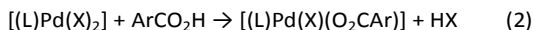b. *Department of Chemistry, Faculty of Science, Central Tehran Branch, Islamic Azad University, Shahrak Gharb, Tehran, Iran. Email: ariafard@yahoo.com*
c. *School of Physical Sciences, University of Tasmania, Hobart, Tasmania 7001, Australia*

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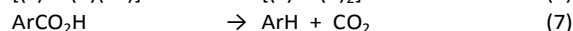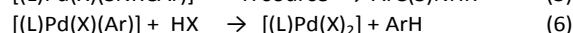
To model the key decarboxylation and insertion steps associated with transformation of coordinated benzoate to coordinated thiobenzamides shown in Scheme 1, the two DMSO ligands were replaced by the phen ligand and loss of the anionic group X provided the requisite charge for the MS studies. Thus eqs 3 and 4 below were investigated using multistage mass spectrometry (MS) experiments and DFT calculations (Figure 1).

$$[(L)Pd(X)_2] + ArCO_2H \rightarrow [(L)Pd(X)(O_2CAr)] + HX \quad (2)$$
$$[(phen)Pd(O_2CPh)]^+ \rightarrow [(phen)Pd(Ph)]^+ + CO_2 \quad (3)$$
$$[(phen)Pd(Ph)]^+ + RNCS \rightarrow [(phen)Pd(SNRCPh)]^+ \quad (4)$$

The complex $[(phen)Pd(O_2CC_6H_5)]^+$ (phen = 1,10-phenanthroline) can be generated by electrospray ionization (ESI) and decarboxylated upon collision-induced dissociation (CID) to yield $[(phen)Pd(C_6H_5)]^+$. Decarboxylation proceeds via **TS7-8**, transforming the chelating benzoate, **7**, to reactive conformation **8**, that yields $[(phen)Pd(C_6H_5)(OCO)]^+$ **9** through **TS8-9** (Figure 1B). Loss of CO_2 gives the putative three-coordinate complex $[(phen)Pd(C_6H_5)]^+$ **10**,[16] which readily reacts with MeNCS (Figure 1C, eq. 4) to form $[(phen)Pd(SC(NMe)C_6H_5)]^+$ at a rate of 2.03 $cm^3 \cdot molecules^{-1} \cdot s^{-1}$. The identity of the the C-C bond coupled product was confirmed as $[(phen)Pd(SC(NMe)C_6H_5)]^+$, rather than $[(phen)Pd(C_6H_5)-(MeNCS)]^+$, by comparing the CID spectra of the ion-molecule reaction product with the CID spectra of an authentic sample of the Pd^{2+} complex of N-methylbenzothioamide prepared by a standard Grignard reaction (Figure S1). A similar reaction (rate of 2.99 $cm^3 \cdot molecules^{-1} \cdot s^{-1}$) is observed for PhNCS. Both reactions are highly efficient, proceeding at the collision rate. DFT calculations predict that these reactions are highly exothermic,

and occur through isothiocyanate insertion into the Pd-C bond to give the coordinated thioamides, $[(phen)Pd(SC(NR)C_6H_5)]^+$ (Figures 1D and S2). DFT calculations also predict these reactions could be considered the reverse of decarboxylation (Figure 1B), initially forming $[(phen)Pd(C_6H_5)(SCNR)]^+$ **11**, which then undergoes insertion via **TS11-12** to give S-coordinated thioamide, **12**, which isomerises to **13** via **TS12-13** (Figure 1D).

Stimulated by the proof of concept gas-phase studies, we explored the conversion of aromatic carboxylic acids into thioamides using a stoichiometric amount of palladium acetate. Individual reaction steps shown in Scheme 1 (eqs 2 – 5) were examined via ^1H NMR spectroscopy. Successful conversion relies on the insertion reaction (eq. 4) being faster than protonation of the organometallic (eq. 6) that leads to protodecarboxylation (eq. 7).

$$[(L)Pd(X)(SNRCAr)]^+ + \text{“H source”} \rightarrow ArC(S)NHR \quad (5)$$
$$[(L)Pd(X)(Ar)] + HX \rightarrow [(L)Pd(X)_2] + ArH \quad (6)$$
$$ArCO_2H \rightarrow ArH + CO_2 \quad (7)$$

Guided by Kozlowski's detailed mechanistic study on protodecarboxylation,[13] ^1H NMR was used to monitor the transformation of 2,6-dimethoxybenzoic acid to N-alkyl-2,6-dimethoxythiobenzamide using $Pd(O_2CCH_3)_2$ in d_6-DMSO (Figures S3-7). Formation of $[(DMSO)_nPd(O_2CCH_3)(O_2CAr)]$ results in an upfield shift of the resonances attributed to the para- proton from δ 7.30 to 7.18 ppm (Figure S4b). Heating the reaction mixture at 65°C for 4 hours results in decarboxylation and the formation of the organometallic complex $[(DMSO)_2Pd(O_2CCH_3)(Ar)]$ (Figure S4c, eq. 3), and results in a further upfield shift of H_{para} to 7.01 ppm with concomitant peak broadening. Continued heating for 24 hours leads to
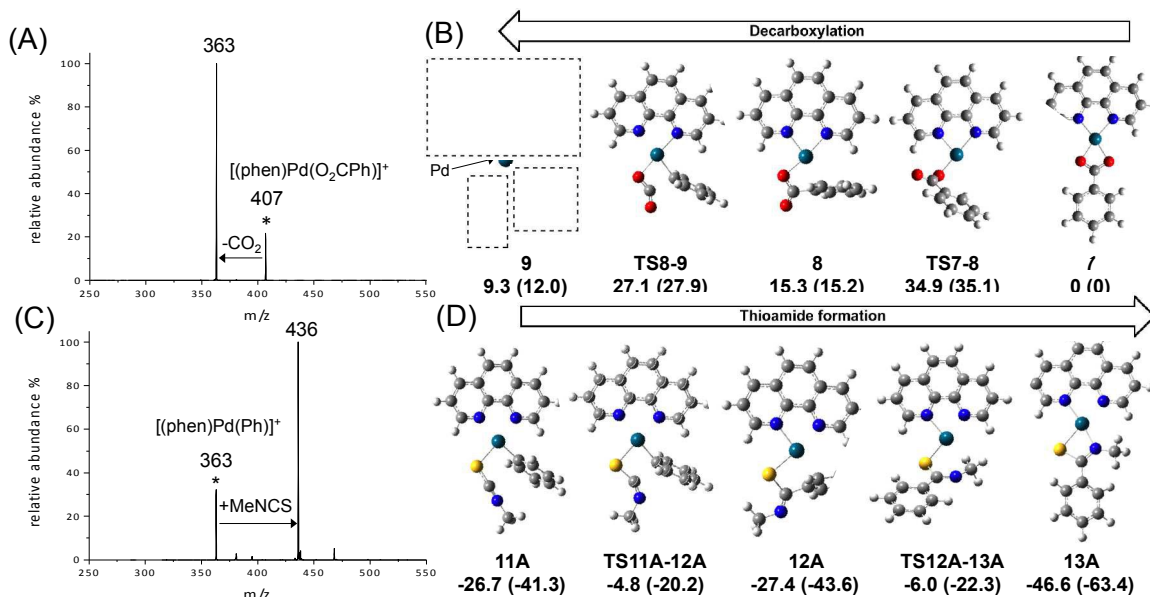

Figure 1. Gas-phase experiments (LTQ ion trap) and DFT calculations (B3LYP-gd3bj/SDD6-31+G(d)//M06/SDD6-31+G(d)) on: **(A,B)** decarboxylation (eq. 3, ΔG = 10.8 kcal/mol, ΔH = 23.7 kcal/mol, MS^2 CID, normalised collision energy of 14% and reaction time of 10ms); **(C,D)** insertion of MeNCS into the Pd-C bond (eq. 4, MS^3 IMR, concentration of MeNCS is 2.8 x 10^9 molecule/cm^3 and reaction time is 250 ms). DFT calculated species are orientated to highlight the direct relationship between carbon dioxide extrusion and isothiocyanate insertion for isoelectronic CO_2 and SCNR. Relative Gibbs and enthalpy energies (in parentheses, in kcal/mol). For (B) and (D) carbon = grey, nitrogen = blue, oxygen= red, palladium = turquoise, sulphur = yellow.

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formation of 1,3-dimethoxybenzene (Figure S4d, eq. 6), corresponding to the last step of the undesired protodecarboxylation reaction (eq. 7). In contrast, if RNCS is added at room temperature to [(DMSO)$_2$Pd(O$_2$CCH$_3$)(Ar)], the coordinated thioamidate is formed (Figure S4e, eq 4). The resultant NMR spectrum is complex, likely due to different coordination modes of the thioamidate to the Pd centre. The free thioamide is formed following reaction with NaBH$_4$ (Figure S4f, eq. 5). The overall process of insertion followed by reaction with NaBH$_4$ results in a downfield shift of the H_{para} proton (7.01 to 7.24 ppm, Δδ = 0.23 ppm) indicating the transformation to the thioamide. The identity of the thioamide was also confirmed by ESI-MS analysis of the NMR sample. Insertion is sensitive to the nature of the alkyl group of the isothiocyanate, RNCS (Figures S4-7). Conversion to the thioamide occurs at 1 hour for R = Me, Et and *i*Pr, but requires 4 hours for R = *t*Bu. Relative yields for thioamide formation versus protodecarboxylation were: ≈ 80% for R = Me, Et and *i*Pr and ≈ 50% for R = *t*Bu, consistent with the longer reaction time required when R = *t*Bu.

The effect of replacing the phen ligand used in the MS experiments with coordinated DMSO was investigated by DFT calculations.[17] It is possible for the [Pd(DMSO)$_2$] complexes to exists as either *cis* or *trans* isomers (Figures S41-44). The presence of a 'reservoir' of acetic acid in solution (absent in the gas-phase) can lead to the formation of 1,3-dimethoxybenzene so competition between insertion and protonation of the organopalladium was considered. The solvation effect of DMSO on the optimised structures required the use of a conductor polarizable continuum model (CPCM). The reactivity of **14** for insertion of MeNCS and protonation was considered by DFT (Figure 2). Insertion starts with a simple associative substitution reaction in which one of the coordinating O atoms of the bidentate acetate ligand is

replaced by a sulfur atom of the isothiocyanate, **TS$_{14-15}$,** to give κ^1-acetate complex **15** followed by the insertion of MeNCS into the Pd-Ar bond to afford **16**. An alternative orientation of MeNCS in **TS$_{15-16'}$** is higher in energy. For protonation, **14** is substituted by acetic acid to form κ^1-acetate intermediate **17**. Proton transfer forms **18**. The transition structures for insertion and protonation steps (**TS$_{15-16}$** and **TS$_{17-18}$,** respectively) both lie lower in energy than those for substitution. **TS$_{14-15}$** is more stable than **TS$_{14-17}$** by 1.1 kcal/mol, suggesting that the insertion reaction would be faster than protonation, a result substantiated by the NMR studies. DFT calculations revealed how the nature of the R groups of RNCS affects the ease of the insertion process (Scheme S3). The **TS$_{15-16}$** is always more stable than **TS$_{15-16'}$** and the energy barrier dependence of the RNCS substitution (**TS$_{14-15}$**) on the R group is insignificant. The insertion transition structure (**TS$_{15-16}$**) is lower in energy than **TS$_{14-15}$**, with the exception of R = *t*Bu, so the chemoselectivity is dictated by the substitution. For R = *t*Bu, the steric repulsion between the *t*Bu substituent and the aryl ligand in **TS$_{15-16}$** results in this transition structure being destabilised considerably and lies above **TS$_{14-15}$**. Thus, for R = *t*Bu, the insertion step, and not substitution, is likely to play the crucial role in determining the chemoselectivity. Thus the insertion and protonation pathways become more competitive, which explains the slow reaction of **14** with *t*BuNCS observed experimentally.

The reaction scope was investigated with different RNCS substrates (Table 1). The resulting N-aryl(alkyl)-2,6-dimethoxythiobenzamide products were characterised by HRMS, ^{1}H and ^{13}C NMR spectroscopy (Figures S8-25) and, where possible X-ray crystallography (Figures S26-40). The acetic acid formed in eq. 2 can promote protonation (eq. 6) or other side-reactions so for the reactions with aryl isothiocyanates, K$_2$CO$_3$ was added after decarboxylation. The
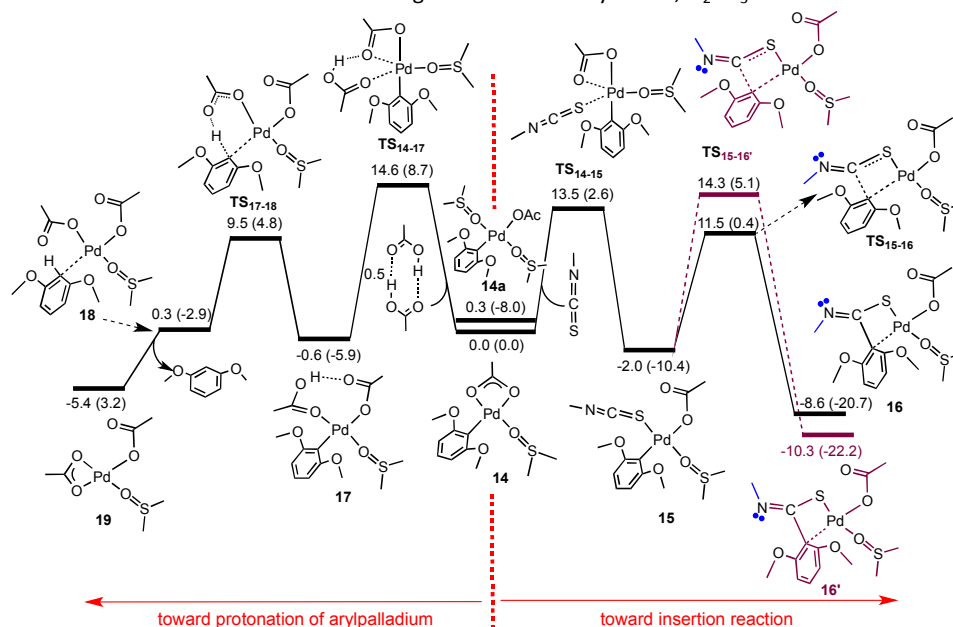
Figure 2 Energy profile showing competition between protonation and insertion of MeNCS for [(DMSO)Pd(O$_2$CCH$_3$)(Ar)], **14**. Relative Gibbs and enthalpy energies (in parentheses) are given in kcal/mol, calculated at the B3LYP-D3BJ/BS3//M06/BS1 level of theory in DMSO using the CPCM approach.

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faster insertion of alkyl isothiocyanates meant that addition of base was not required. Following addition of $NaBH_4$ products **6a-c** could be isolated in modest yields (47-57%, Table 1, entries 1-3). The reaction with sterically demanding *t*BuNCS required a longer reaction time, resulting in more protodecarboxylated and amide products as compared to thioamide **6d**. Addition of K_2CO_3 after decarboxylation is essential for reactions with arylisothiocyanates to prevent partial conversion of the thioamides to amides (identified by ESI-MS and isolated and characterised by ^{1}H NMR for 2,6-dimethoxy-N-phenylbenzamide, Figures S13 & S22). While the exact mechanism of this transformation is unknown, soft metal ions such as Pd^{2+} promote hydrolysis of thioamides to amides[18] and amides have been noted as unwanted side products in palladium catalysed transformations of thioamides.[19] In the case of PhNCS, the yield of **6e** improved with the use of both K_2CO_3 and $NaBH_4$ (Table 1). The yield of isolated thioamide was found to depend on the "H" source added. Addition of 5 equiv. of $NaBH_4$ gave the optimum yield of **6f** and **6g**. The potential reduction of the nitro functional group in **6h** was avoided by not including a "H" source.

In summary, a mechanism-based approach using gas-phase ion chemistry was used to uncover a new transformation of aromatic carboxylic acids to substituted thioamides. This same transformation can be readily achieved as a "one-pot" method in solution using stoichiometric amounts of organic precursors and palladium acetate. Preliminary studies suggest that a range of other aryl carboxylates can be used as substrates.[20] The two crucial steps of decarboxylation of the coordinated carboxylate in $[(phen)Pd(O_2CC_6H_5)]^+$ (eq. 3) and insertion of the isothiocyanate into the Pd-C bond of $[(phen)Pd(C_6H_5)]^+$ (eq. 4) are directly related to each other by the isoelectronic nature of CO_2 and RNCS. MacMillan has recently classified decarboxylation reactions in which two fragments recombine as CO_2ExR (ExR = Extrusion-Recombination).[21] By analogy, the chemistry described here is part of group of CO_2ExIn (ExIn = Extrusion-Insertion) reactions.[22] It is possible that this approach is compatible with other small molecules that are isoelectronic with CO_2 and this is currently under investigation.

Table 1 Isolated yields for the synthesis of thioamides **6a-h** ([a]reaction in the absence of K_2CO_3).

Entry	Product, R	$NaBH_4$ (equiv)	Yield (%)
1	**6a**, Me	$NaBH_4$ (5)[a]	47
2	**6b**, Et	$NaBH_4$ (5)[a]	50
3	**6c**, iPr	$NaBH_4$ (5)[a]	57
4	**6d**, tBu	$NaBH_4$ (5)[a]	12
5	**6e**, Ph	$NaBH_4$ (5)	60
6	**6f**, *p*ClPh	$NaBH_4$ (5)	53
7	**6g**, *p*CF$_3$Ph	$NaBH_4$ (5)	40
8	**6h**, *p*NO$_2$Ph	None	22

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