Tetrahedron Letters 51 (2010) 5341–5343

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted palladium-catalysed carbonylations of aryl and heteroaryl halides with sulfamide nucleophiles utilising a solid CO source

David Liptrot, Lilian Alcaraz, Bryan Roberts *

Department of Chemistry, AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leics, LE11 5RH, United Kingdom

ARTICLE INFO

Article history:
Received 18 July 2010
Accepted 3 August 2010
Available online 9 August 2010

Keywords:
Carbonylation
Palladium
Homogeneous catalysis
Microwave chemistry
Sulfamides
Acyl sulfamides

ABSTRACT

$Mo(CO)_6$ acts as a source of carbon monoxide for the palladium-catalysed, microwave-assisted, carbonylative coupling of aryl or heteroaryl halides with sulfamide nucleophiles to yield aryl and heteroaryl acyl sulfamides.

The acyl sulfamide functional group (Fig. 1) is a useful functional group in the field of medicinal chemistry. When R^3 = H, the acyl sulfamide is acidic and can serve as a suitable bioisostere for phenols, carboxylic acids, sulfonic acids and acyl sulfonamides.[1] Recently acyl sulfamide structures have been reported as HCV protease inhibitors,[2] CXCR2 antagonists[3] and aryl acyl sulfamide structures have been disclosed in a number of pharmaceutical patents as potential therapeutic agents with wide ranging biological activities.[4]

To date, methods for the preparation of aryl acyl sulfamides involve activation of a precursor carboxylic acid with a suitable coupling agent and reaction with an appropriately substituted sulfamide.[5] The yields of product obtained using these methods are dependent on the choice of coupling agent and substituted sulfamide used. The scope of these transformations is often limited by the availability of the precursor carboxylic acids, which can in some cases be difficult to handle and isolate, or are prone to rapid decarboxylation. To address this issue we recently reported a new route to aryl and heteroaryl acyl sulfamides via palladium-catalysed carbonylation of aryl and heteroaryl halides with sulfamides utilising microwave irradiation and vials pre-pressurised with carbon monoxide gas.[6] This method is simple and efficient with wide substrate scope but does require the use of specialised carbonylation equipment which is not available in all laboratories. Furthermore the method is not easily adaptable to parallel synthesis and automation, often required in modern medicinal chemistry laboratories. The palladium-catalysed $Mo(CO)_6$-mediated carbonylative coupling of aryl and heteroaryl halides with a variety of nucleophiles under microwave-assisted conditions is now well established in the literature and ideally suited to small scale laboratory reactions, parallel synthesis and semi-automation.[7] Herein we report the first synthesis of aryl and heteroaryl acyl sulfamides via palladium-catalysed carbonylation using $Mo(CO)_6$ as the CO source. We began by examining the reaction shown in Table 1. Using iodobenzene as a model aryl halide, for reactions with sulfamide **1a**, DBU as base, 1,4-dioxane, $Mo(CO)_6$ and $Pd(OAc)_2$, an optimisation of the reaction was performed in the microwave with respect to time and temperature. Unfortunately, at temperatures below 140 °C poor conversion to product was observed even with extended reaction times (5 h). At temperatures above 140 °C isolated yields of product were low due to competing pyrrolidine amide formation, resulting from decomposition of the sulfamide under basic conditions to yield the more nucleophilic amine (Scheme 1).[8]

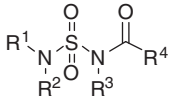


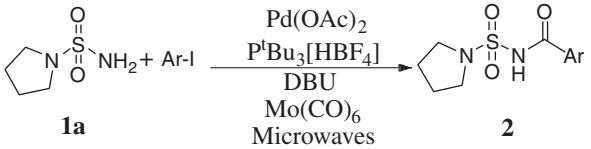
Figure 1. The acyl sulfamide functional group.

After screening several phosphine ligands it was found that addition of $P^tBu_3[HBF_4]$, a temperature of 100 °C and a reaction time of 2 h gave complete conversion of iodobenzene and afforded the desired acyl sulfamide in 87% yield (Table 1, entry 1). The

* Corresponding author. Tel.: +44 12509 644 542; fax: +44 1509 645 571.
E-mail address: bryan.roberts@astrazeneca.com (B. Roberts).

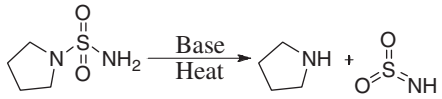
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2010.08.009

Table 1
Reaction between aryl iodides and sulfamide **1a**[a]



Entry	Ar-I	Acyl sulfamide	Yield[b] (%)
1	C_6H_5-I	**2a**	87
2	3-Cl-C_6H_4-I	**2b**	92
3	4-MeO-C_6H_4-I	**2c**	93
4	4-NC-C_6H_4-I	**2d**	94
5	3-Thienyl-I	**2e**	94

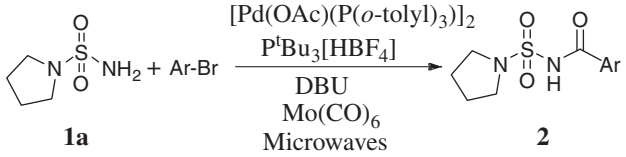
[a] Reaction conditions: aryl iodide (1 mmol), sulfamide **1a** (2 mmol), $Pd(OAc)_2$ (0.1 mmol), $P^tBu_3[HBF_4]$ (0.2 mmol), DBU (3 mmol), $Mo(CO)_6$ (1 mmol) in 1,4-dioxane (3 mL), microwave heated in a sealed tube to 100 °C for 2 h.
[b] Isolated and purified.



Scheme 1. The formation of amines from sulfamides under basic conditions at elevated temperatures.

reaction conditions were then applied to a small set of aryl iodides (Table 1). Electron-donating and electron-withdrawing groups on the aryl ring (Table 1, entries 2–4) and heteroaromatic iodides (Table 1, entry 5) all gave excellent yields. Attempts to apply this method to aryl bromides were unsuccessful. Thus we sought conditions for the more widely available aryl bromides. Guided by literature precedent,[9] we examined the reaction shown in Table 2.

Table 2
Reaction between aryl bromides and sulfamide **1a**[a]

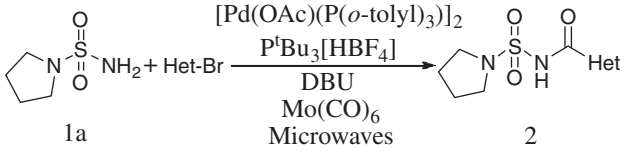


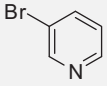
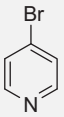
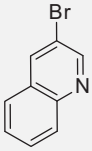
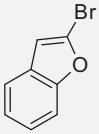
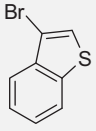
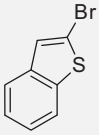
Entry	Ar-Br	Acyl sulfamide	Yield[b] (%)
1	C_6H_5-Br	**2a**	78
2	3-Cl-C_6H_4-Br	**2b**	90
3	3-MeO-C_6H_4-Br	**2f**	88
4	3-F_3C-C_6H_4-Br	**2g**	68
5	3-NC-C_6H_4-Br	**2h**	74
6	3-Me-C_6H_4-Br	**2i**	72
7	4-Cl-C_6H_4-Br	**2j**	77
8	4-MeO-C_6H_4-Br	**2c**	88
9	4-F_3C-C_6H_4-Br	**2k**	73
10	4-$Me_2NC(O)$-C_6H_4-Br	**2l**	86
11	4-NC-C_6H_4-Br	**2d**	50
12	4-^{t}Bu-C_6H_4-Br	**2m**	53
13	2-Naphthyl-Br	**2n**	70
14	2-Cl-C_6H_4-Br	**2o**	20 (56[c])
15	2-F-C_6H_4-Br	**2p**	78
16	2-MeO-C_6H_4-Br	**2q**	0[d] (68[c])
17	2-Me-C_6H_4-Br	**2r**	0[d] (60[c])

[a] Reaction conditions: aryl bromide (1 mmol), sulfamide **1a** (2 mmol), $[Pd(OAc)(P(o\text{-tolyl})_3)]_2$ (0.1 mmol), $P^tBu_3[HBF_4]$ (0.2 mmol), DBU (3 mmol), $Mo(CO)_6$ (1 mmol) in 1,4-dioxane (3 mL), microwave heated in a sealed tube to 100 °C for 2.5 h.
[b] Isolated and purified.
[c] DMAP (1 mmol) added.
[d] 10–20% product in reaction mixtures by HPLC/MS—reactions not progressed.

Using bromobenzene as a model aryl halide, for reactions with sulfamide **1a**, DBU, 1,4-dioxane, $Mo(CO)_6$, $[Pd(OAc)(P(o\text{-tolyl})_3)]_2$ and $P^tBu_3[HBF_4]$ as the ligand, an optimisation of the reaction was performed in the microwave with respect to time and temperature. A reaction time of 2.5 h and a temperature of 100 °C gave complete conversion of bromobenzene and afforded the desired acyl sulfamide in 78% yield (Table 2, entry 1). The reaction conditions were then applied to a range of aryl bromides. (Table 2). A wide range of *meta*- and *para*-substituted aryl bromides performed well in the reaction giving moderate to excellent yields (Table 2, entries 2–12). It is also worth noting the complete chemoselectivity for bromine over chlorine in the reaction (Table 2, entries 2 and

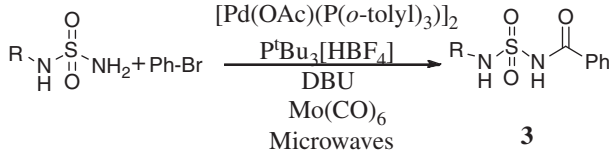
Table 3
Reaction between heteroaryl bromides and sulfamide **1a**[a]

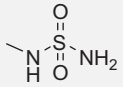
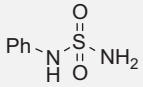
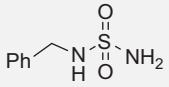


Entry	Het-X	Acyl sulfamide	Yield[b] (%)
1		**2s**	84
2		**2e**	51
3		**2t**	58
4		**2u**	74
5		**2v**	46[c]
6		**2w**	76[c]
7		**2x**	52[c]
8		**2y**	87
9		**2z**	55

[a] Reaction conditions: heteroaryl bromide (1 mmol), sulfamide **1a** (2 mmol), $[Pd(OAc)(P(o\text{-tolyl})_3)]_2$ (0.1 mmol), $P^tBu_3[HBF_4]$ (0.2 mmol), DBU (3 mmol), $Mo(CO)_6$ (1 mmol) in 1,4-dioxane (3 mL), microwave heated in a sealed tube to 100 °C for 2.5 h.
[b] Isolated and purified.
[c] Workup modified to tolerate basic N atom.

Table 4
Reaction between bromobenzene and substituted sulfamides[a]



Entry	Sulfamide	Acyl sulfamide	Yield[b] (%)
1		**3a**	91
2		**3b**	72
3		**3c**	59

[a] Reaction conditions: bromobenzene (1 mmol), substituted sulfamide (2 mmol), $[Pd(OAc)(P(o\text{-tolyl})_3)]_2$ (0.1 mmol), $P^tBu_3[HBF_4]$ (0.2 mmol), DBU (3 mmol), $Mo(CO)_6$ (1 mmol) in 1,4-dioxane (3 mL), microwave heated in a sealed tube to 100 °C for 2.5 h.
[b] Isolated and purified.

7). Fused aryls also performed well in the reaction (Table 2, entry 13). It should be noted that *ortho*-substituted aryl bromides gave poor yields with substituents any larger than fluorine. We believe that this is due to steric effects around the intermediate acyl palladium species. Based on precedent from the literature,[10] and our previous experience of using DMAP as an acyl transfer reagent, we found that addition of DMAP to these reactions improved the yields (Table 2, entries 14, 16 and 17). Attempts to apply these methods to both electron-rich and electron-poor aryl chlorides, even with extended reaction times and increased temperatures met with no success. This is not too surprising since there are few literature reports for using aryl chlorides in the palladium-catalysed $Mo(CO)_6$-mediated carbonylative coupling. Larhed and Lagerlund[11] have reported the formation of benzamides from aryl chlorides via palladium-catalysed $Mo(CO)_6$-mediated carbonylative coupling but this method required temperatures of 170 °C which in our reactions leads to sulfamide decomposition.

Having had success with a wide range of aryl bromides we turned our attention to heteroaryl bromides. Gratifyingly the conditions optimised for aryl bromides gave moderate to good isolated yields of heteroaryl acyl sulfamides without further optimisation (Table 3). This methodology is applicable to a wide range of heterocycles such as five-membered furans and thiophenes (Table 3, entries 1–3), six-membered pyridines (Table 3, entries 4 and 5), and fused five- and six-membered heterocycles (Table 3, entries 6–9). It should be noted that basic heterocycles required moderately different workup conditions to non-basic as described in the Supplementary data.

Finally, a small set of sulfamides was synthesised[12] and utilised in the coupling with bromobenzene without any further optimisation (Table 4). Good to excellent isolated yields of acyl sulfamides were obtained with a range of substituted sulfamides; alkyl-, phenyl- and benzyl-substituted sulfamides all performed well in the reaction (Table 4, entries 1–3). It is worth noting that in all these cases complete regioselectivity was observed with the reaction taking place on the least substituted nitrogen. This, we speculate, is once again due to steric effects around the intermediate aryl acyl palladium species.

In summary, we have developed a new, practical and efficient route to aryl and heteroaryl acyl sulfamides via palladium-catalysed $Mo(CO)_6$-mediated carbonylative coupling of readily available aryl and heteroaryl halides in the presence of sulfamides. The protocol should find broad application for the synthesis of a wider variety of aryl and heteroaryl acyl sulfamides than currently accessible through the known methodologies. We also believe that this reaction complements our recently disclosed report of using CO gas for this reaction, in that no specialised gas handling carbonylation equipment is required thus enabling the reactions to be carried out in parallel or in a semi-automated manner.

Acknowledgements

We are grateful to Sara Griffiths and Richard Evans both of AstraZeneca Charnwood Chemistry Department for their expert assistance with MS studies and microwave equipment, respectively.

Supplementary data

Supplementary data (further experimental procedures and full characterisation for all newly synthesised compounds. *Caution*: $Mo(CO)_6$ is toxic and the heating of sealed vessels should only be performed using the appropriate equipment) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.009.

References and notes

1. (a) Stocks, M.; Alcaraz, L. In *On Medicinal Chemistry*; Griffen, E., Ed., 1st ed.; Sci.Ink: Oxford, 2007; (b) *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed., 2nd ed.; Academic Press: London, 2003; (c) Albright, J. D.; DeVries, V. G.; Du, M. T.; Largis, E. E.; Miner, T. G.; Reich, M. F.; Shepherd, R. G. *J. Med. Chem.* **1983**, *26*, 1393.
2. Raboisson, P. J. B.; Hu, L.; Vendeville, S.; Nyanguile, O. WO Filing 2009080836, 2009; *Chem. Abst.* **2009**, *151*, 124047.
3. Winters, M. P.; Crysler, C.; Subasinghe, N.; Ryan, D.; Leong, L.; Zhao, S.; Donatelli, R.; Yurkow, E.; Mazzulla, M.; Boczon, L.; Manthey, C. L.; Molloy, C.; Raymond, H.; Murray, L.; McAloman, L.; Tomczuk, B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1926.
4. Reitz, A. B.; Smith, G. R.; Parker, M. H. *Expert Opin. Ther. Patents* **2009**, *19*, 1449.
5. (a) For selected examples from recent literature see: Gentles, R. G.; Ding, M.; Hewawasam, P. U.S. Patent 2007275930, 2007; *Chem. Abst.* **2007**, *148*, 11085.; (b) Schmidt, T.; Gebhardt, J.; Loehr, S.; Keil, M.; Wevers, J. H.; Rack, M.; Mayer, G.; Pleschke, A. WO Filing 2007063028, 2007; *Chem. Abst.* **2007**, *147*, 52713.; (c) Ravindranadh, V.; Somu, H.; Boshoff, H.; Qiao, C.; Bennett, E. M.; Clifton, E.; Barry, C. E., III; Aldrich, C. C. *J. Med. Chem.* **2006**, *49*, 31.
6. Roberts, B.; Liptrot, D.; Alcaraz, L. *Org. Lett.* **2010**, *12*, 1264.
7. (a) Georgson, J.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2003**, *5*, 350; (b) Wu, X.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 346; (c) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327; (d) Wannberg, J.; Dallinger, D.; Kappe, C. O.; Larhed, M. *J. Comb. Chem.* **2005**, *7*, 574; (e) Wannberg, J.; Kaiser, N. F. K.; Vrang, L.; Samuelsson, B.; Larhed, M.; Hallberg, A. *J. Comb. Chem.* **2005**, *7*, 611; (f) Wu, X.; Ekegren, J. K.; Larhed, M. *Organometallics* **2006**, *25*, 1434; (g) Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* **2006**, *62*, 4665.
8. During the course of our work with sulfamides we have observed that they can undergo base catalysed thermal decomposition to release the corresponding amine. Alcaraz, L.; Bennion, C.; Morris, J.; Meghani, P.; Thom, S. M. *Org. Lett.* **2004**, *6*, 2705; This has also previously been reported in the literature: Kavalek, J.; Kralikova, U.; Machacek, V.; Seldlak, M.; Sterba, V. *Collect. Czech. Chem. Commun.* **1990**, *55*, 202.
9. Wu, X.; Rönn, R.; Gossas, T.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 3094.
10. Odell, L. R.; Sävmarker, J.; Larhed, M. *Tetrahedron Lett.* **2008**, *49*, 6115.
11. Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4.
12. Winum, J.-Y.; Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J. L. *Org. Lett.* **2001**, *3*, 2241.