ORGANIC LETTERS

2010
Vol. 12, No. 6
1264−1267

Novel Aryl and Heteroaryl Acyl Sulfamide Synthesis via Microwave-Assisted Palladium-Catalyzed Carbonylation

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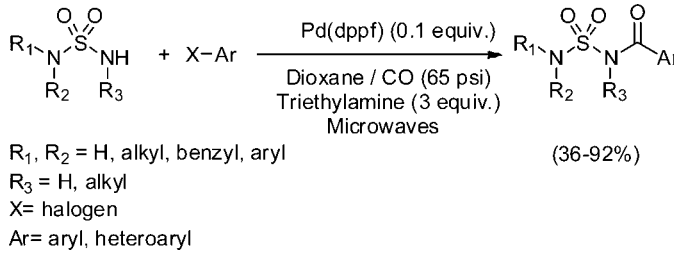
Received January 20, 2010

ABSTRACT



A novel, simple synthesis of aryl and heteroaryl acyl sulfamides has been developed via palladium-catalyzed carbonylation of aryl or heteroaryl halides in the presence of sulfamide nucleophiles. A range of reactions illustrating the wide scope of this reaction was carried out under microwave irradiation in a vessel equipped with a gas inlet adapter and proceeded in good to excellent yields.

The sulfamide functional group **1** is not as widely represented in the area of medicinal chemistry as either the urea or sulfonamide functional groups (Figure 1). However, over the past decade, it has found use in many applications in the field of medicinal chemistry.[1,2] The sulfamide group can act as a useful bioisosteric replacement for sulfamate, sulfonamide, carbamate, amide, and phenol functionalities.[3] Attachment of an acyl group to the sulfamide group gives the more acidic acyl sulfamides **2**, which can serve as bioisosteric replacements for carboxylic acids, sulfonic acids, and phenols.[3] Over the past few years an increasing number of patents have disclosed aryl acyl sulfamide structures as potential therapeutic agents with diverse biological activities.[4] To date, the only available 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 scope of

(1) For selected examples from recent literature see: (a) Avalle, P.; Foley, J. R.; Mullens, P.; Wang, Y.; Yehl, P. *Chem. Abstr.* **2009**, *151*, 173453; US-2009182002, 2009. (b) Harrison, R. J.; Major, J.; Middlesmiss, D.; Ramsden, N.; Kruse, U.; Drewes, G. *Chem. Abstr.* **2009**, *151*, 10194; WO-2009080638, 2009. (c) Shibata, T.; Iwataru, H.; Kiga, M.; Shimazaki, N.; Echigo, Y.; Fujiwara, K.; Tanzawa, F. *Chem. Abstr.* **2006**, *144*, 331427; JP-2006083133, 2006. (d) Zhong, J.; Gan, X. *Bioorg. Med. Chem.* **2004**, *12*, 589–593. (e) Collins, I. J.; Cooper, L. C. *Chem. Abstr.* **2003**, *139*, 381492; WO-2003093264, 2003. (f) Kadow, J. F.; Regueiro-Ren, A.; Xue, Q. M. *Chem. Abstr.* **2003**, *140*, 59662; WO-2004000210, 2003. (g) Cherney, R. J.; King, B. W. *Chem. Abstr.* **2002**, *136*, 309923; WO-2002028846, 2002. (h) Schaal, W.; Karlsson, A.; Ahlsén, G.; Lindberg, J.; Andersson, H. O.; Danielson, U. H.; Classon, B.; Unge, T.; Samuelsson, B.; Hultén, J.; Hallberg, A.; Karlén, A. *J. Med. Chem.* **2001**, *44*, 155–169. (i) Groutas, W. C.; He, S.; Kuang, R.; Ruan, S.; Tu, J.; Chan, H.-K. *Bioorg. Med. Chem.* **2001**, *9*, 1543–1548.

(2) Bolli, M.; Boss, C.; Fischli, W.; Clozel, M.; Weller, T. *Chem. Abstr.* **2002**, *137*, 93766; WO-2002053557, 2002.

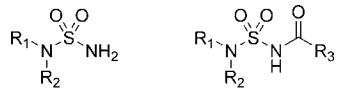
(3) (a) *On Medicinal Chemistry*, 1sr ed.; Stocks, M., Alcaraz, L., Griffen, E., Eds.; Sci.Ink: Oxford, UK, 2007. (b) *The Practice of Medicinal Chemistry*, 2nd ed.; Wermuth, C. G., Ed.; Academic Press: London, UK, 2003. (c) Albright, J. D.; DeVries, V. G.; Du, M. T.; Largis, E. E.; Miner, T. G.; Reich, M. F.; Shepherd, R. G. *J. Med. Chem.* **1983**, *26*, 1393–1411.

(4) Reitz, A. B.; Smith, G. R.; Parker, M. H. *Expert Opin. Ther. Pat.* **2009**, *19*, 1449–1452.

(5) For selected examples from recent literature see: (a) Gentles, R. G.; Ding, M.; Hewawasam, P. *Chem. Abstr.* **2007**, *148*, 11085; US-2007275930, 2007. (b) Schmidt, T.; Gebhardt, J.; Loehr, S.; Keil, M.; Wevers, J. H.; Rack, M.; Mayer, G.; Pleschke, A. *Chem. Abstr.* **2007**, *147*, 52713; WO-2007063028, 2007. (c) Ravindranadh, V.; Somu,; Boshoff, H.; Qiao, C.; Bennett, E. M.; Clifton, E.; Barry, C. E., III; Aldrich, C. C. *J. Med. Chem.* **2006**, *49*, 31–34.

10.1021/ol100083w
Published on Web 02/11/2010

these transformations is limited by the availibility of the required precursor acids which can, in some cases, be difficult to handle and isolate. With the increasing use of aryl acyl sulfamides in medicinal chemistry, we decided to investigate the development of alternative methodologies for their synthesis.



1 2

Figure 1. Sulfamide **1** and acyl sulfamide **2** functional groups

In 1974, Heck and co-workers reported the first use of a palladium-catalyzed reaction of carbon monoxide, aryl halides, and alcohols or amines as nucleophiles to give the respective benzoate and benzamide products.[6] Since then the scope of the palladium-catalyzed carbonylation reaction has been developed such that a wide range of nucleophiles can now be used, enabling the efficient synthesis of numerous carbonyl derivatives.[7,8]

To the best of our knowledge the synthesis of aryl and heteroaryl acyl sulfamides via palladium-catalyzed carbonylation is unprecedented in the literature. We hereby report the first palladium-catalyzed carbonylation process under microwave irradiation using gaseous carbon monoxide for the synthesis of these compounds of pharmaceutical interest.

Microwave-assisted organic synthesis is an increasingly popular field. The advantages of using microwave irradiation over conventional heating are often a reduction in reaction times and cleaner reactions leading to improved yields.[9]

Recently we acquired a gas inlet adapter allowing us to charge microwave vials with gaseous reagents and heat these prepressurized reaction vessels safely in the microwave.[10] There are few reports in the literature of using prepressurized reaction vials in the microwave. Of interest to us was the work of Kormos and Leadbeater who reported the formation of esters and acids via carbonylation of aryl iodides using carbon monoxide gas in prepressurized reaction vials.[11] Procedures for performing carbonylation reactions with use of microwave heating without the need for using gaseous carbon monoxide have also been reported. These alternative methods rely on the in situ generation of carbon monoxide from molybdenum hexacarbonyl or DMF and formamide.[12] Our results on in situ carbon monoxide generation for this reaction will be published in due course.

We focused our initial investigation on using bromobenzene as a model aryl halide for reactions with sulfamide **1a**, triethylamine as base, 1,4-dioxane as solvent, and $PdCl_2(dppf)\cdot CH_2Cl_2$ as the palladium source. Carbon monoxide pressure was fixed at 65 psi and an optimization of the reaction was carried out in the microwave with respect to time and temperature. A temperature of 100 °C and reaction time of 4 h were found to give complete conversion of bromobenzene and afforded an isolated yield of 92% of the desired acylsulfamide (Table 1, entry 1). We also performed an identical control reaction using conventional oil bath heating. Analysis of the crude HPLC/MS data for the conventional oil bath heating and microwave irradiation reactions indicated comparable results although the microwave reaction did show a cleaner impurity profile. For convenience in our laboratory we chose to use microwave irradiation. To establish the scope of this transformation, these reaction conditions were then applied to a range of aryl halides. The results are summarized in Table 1. A variety of functional groups were tolerated and both electron-donating and electron-withdrawing groups give good isolated yields. It is interesting to note that iodobenzene gave a reduced isolated yield compared with bromobenzene (entries 1 versus 2). Ortho-substituted aryl bromides are well tolerated in the reaction (entries 3−6). However, the more challenging 2-cyclohexylbromobenzene only gave a modest 36% yield (entry 7). Para- (entries 8−12) and meta- (entries 13−16) substitutued systems also performed well in the reaction. In the preceding examples the complete chemoselectivity observed for bromo over chloro is worth noting (entries 5, 11, and 15). Activated aryl chloride did provide a modest isolated yield of product albeit with a longer reaction time (entry 17). However, unactivated 3-methoxychlorobenzene gave unreacted starting material (entry 18). This is not too suprising since carbonylation of aryl chlorides usually requires more forcing conditions, and or alternative palladium catalysts.[13]

Having established a good scope with aryl bromides, application of the method to heteroaryl halides was performed. The results are summarized in Table 2. Gratifyingly the conditions optimized for aryl bromides provided moderate to good isolated yields of heteroaryl acyl sulfamides without further optimization. As shown in Table 2 the methodology is applicable to a wide range of heterocyles such as 5-membered (entries 1−3), 6-membered (entries 4−7), and fused systems (entries 8 and 9). However, once again

(6) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.

(7) Martinelli, J. R.; Donald, A.; Watson, D. M.; Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buckwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102–7107, and references cited within.

(8) For a general review on carbonylation reactions see: Barnard, C. F. J. *Organometallics* **2008**, 5402–5422.

(9) For reviews on microwave chemistry see: (a) *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidstrom, P. Eds.; Blackwell Publishing: Oxford, UK, 2005. (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. (c) Kappe, C. O. Controlled Microwave Heating in Modern Organic Synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.

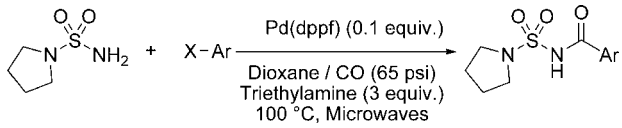
(10) **Experimental setup:** All reactions were performed with a CEM Discover single mode microwave reactor equipped with a 300 W source. A 10 mL fiber optic accessory was equipped with a gas inlet to allow introduction of carbon monoxide gas to the reaction vessel and each of the reactions was performed in a CEM 10 mL microwave reaction vial. All temperature measurements were performed with a fiber optic probe.

(11) (a) Kormos, C. M.; Leadbeater, N. E. *Synlett* **2006**, *11*, 1663–1666. (b) Kormos, C. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 65–68.

(12) For selected examples see: (a) Wan., Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232–6235. (b) Kaiser, N. F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109–111. (c) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750–5753.

(13) Watson, D. A.; Fan, X.; Buckwald, S. L. *J. Org. Chem.* **2008**, *73*, 7096–7101, and references cited within.

Table 1. Pd-Catalyzed Carbonylation of Sulfamide **1a** with Aryl Halides **2a**−**r**[15]



1a **2a-r** **3a-o**

entry		Ar-X **2**	acyl sulfamide **3**	yield (%)[a]
1	**2a**	C_6H_5-Br	**3a**	92
2	**2b**	C_6H_5-I	**3a**	80
3	**2c**	2-Me-C_6H_4-Br	**3b**	83
4	**2d**	2-MeO-C_6H_4-Br	**3c**	73
5	**2e**	2-Cl-C_6H_4-Br	**3d**	61
6	**2f**	2-F-C_6H_4-Br	**3e**	76
7	**2g**	2-Cy-C_6H_4-Br	**3f**	36
8	**2h**	3-MeO_2C-C_6H_4-Br	**3g**	70
9	**2i**	3-Me-C_6H_4-Br	**3h**	83
10	**2j**	3-MeO-C_6H_4-Br	**3i**	82
11	**2k**	3-Cl-C_6H_4-Br	**3j**	76
12	***2l***	3-NC-C_6H_4-Br	**3k**	78
13	**2m**	4-NC-C_6H_4-Br	***3l***	80
14	**2n**	4-MeO-C_6H_4-Br	**3m**	80
15	**2o**	4-Cl-C_6H_4-Br	**3n**	90
16	**2p**	4-Me-C_6H_4-Br	**3o**	75
17	**2q**	4-NC-C_6H_4-Cl	***3l***	54[b]
18	**2r**	3-MeO-C_6H_4-Cl	**3j**	0

[a] Yields quoted are isolated yields. [b] 20 h.

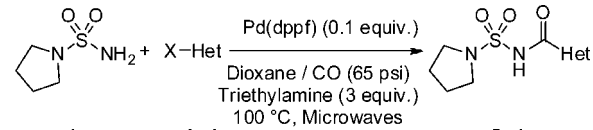
activated heteroaryl chlorides required a longer reaction time to achieve only a modest isolated yield (entry 10).

Turning our attention to the sulfamide partner in these carbonylation reactions, we synthesized a number of substituted sulfamides using known literature methods.[14] Good isolated yields of product were obtained with a range of substituted sulfamides as can be seen in Table 3. Variations of the dialkylated portion of the sulfamide did not significantly affect the outcome of the reaction (entries 1−4). Utilization of sulfamide produced a moderate yield of the desired product (entry 5), whereas a range of monosubstituted alkyl (entries 6−9) and benzyl (entries 10−12) substrates performed well in the reaction. It is worth noting that in all these cases complete regioselectivity was observed with reaction taking place on the least substituted nitrogen. Analysis of these crude reaction mixtures by HPLC/MS revealed no evidence of the presence of the other regioisomers. This regioselectivity is possibly due to steric effects around the intermediate acyl palladium species.

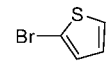
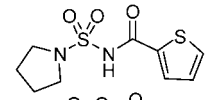
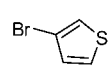
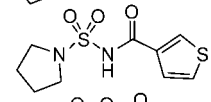
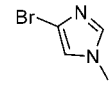
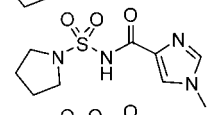
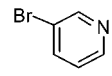
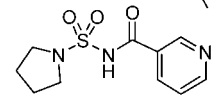
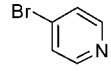
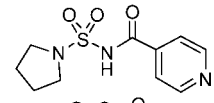
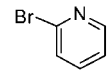
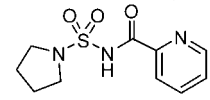
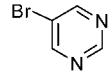
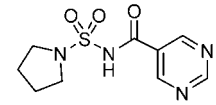
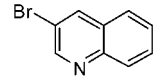
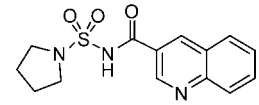
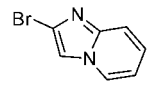
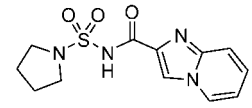
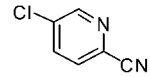
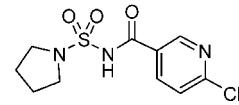
(14) (a) McManus, J. M.; McFarland, J. W.; Gerber, C. F.; McLamore, W. M.; Laubach, G. D. *J. Med. Chem.* **1965**, *8*, 766–776. (b) Aeberli, P.; Gogerty, J.; Houlihan, W. J. *J. Med. Chem.* **1967**, *10*, 636–642. (c) Abdaoui, M.; Dewynter, G.; Aouf, N.; Favre, G.; Morere, A.; Montero, J.-L. *Bioorg. Med. Chem.* **1996**, *4*, 1227–1235. (d) Kavalek, J.; Kralikova, U.; Machacek, V.; Sedlak, M.; Sterba, V. *Collect. Czech. Chem. Commun.* **1990**, *55*, 203–222. (e) Winum, J.-Y.; Toupet, L.; Barragan, V.; Dewynter, G.; Montero, J.-L. *Org. Lett.* **2001**, *3*, 2241–2243.

(15) **General reaction conditions:** sulfamide **1a** (2 equiv), aryl halide (1 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ 10 mol %, triethylamine (3 equiv), 0.3 M dioxane, 4 h, 100 °C, 65 psi CO.

Table 2. Pd-Catalyzed Carbonylation of Sulfamide **1a** with Heteroaryl Halides[15]



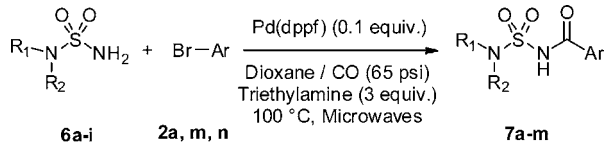
1a **4a-j** **5a-j**

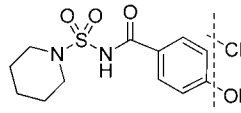
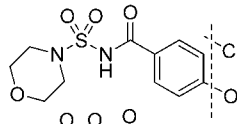
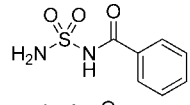
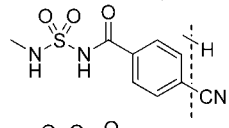
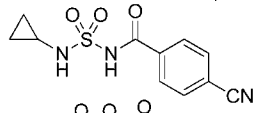
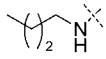
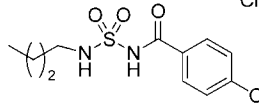
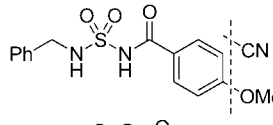
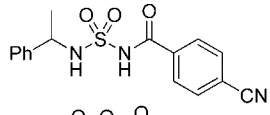
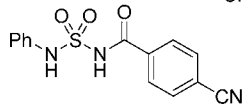
entry	Het - X	product	yield (%)[a]
1			70
2			75
3			50
4			56
5			58
6			66
7			78
8			86
9			72
10			50[b]

[a] Yields quoted are isolated yields. [b] 20 h.

Exploring this effect further, the reaction of trisubstituted sulfamide **8a** with 4-cyanobromobenzene was performed and gave only a 20% isolated yield of product representing a limitation with these reactions conditions (Table 4, entry 1). Other products isolated were the dimethylamide resulting from breakdown of the sulfamide under basic conditions and benzonitrile via unwanted reduction of the aryl bromide.[16] Some reports in the literature suggests that DMAP can act as an acyl transfer reagent reacting readily with the acyl palladium species, to give a sterically less demanding acyl-DMAP derivative, which then reacts with the nucleophile.[17] It was satisfying to note that the addition of DMAP did provide the desired product with a significant increase in

Table 3. Pd-Catalyzed Carbonylation of Sulfamides **6a−i** with Aryl Bromides **2a**, **2m**, and **2n**[15]

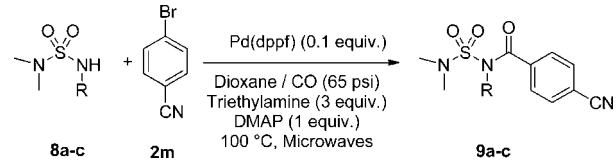


entry	R_1R_2N	Br - Ar	product	yield (%)[a]
1		**2m**		84
2		**2n**		66
3		**2m**		72
4		**2n**		69
5		**2a**		50[b]
6		**2a**		85
7		**2m**		75
8		**2m**		70
9		**2m**		69
10		**2m**		67
11		**2n**		84
12		**2m**		75
13		**2m**		50

[a] Yields quoted are isolated yields. [b] 0.3 M DMF used as solvent instead of dioxane and 3 equiv of sulfamide used.

yield (Table 4, entry 2).[18] Inspired by this result we extended this procedure to a set of trisubstituted sulfamides. As can been seen from the results summarized in Table 4, an increase in the size of the group on the reacting sulfamide nitrogen leads to a proportional decrease in the yield of isolated product (entry 3) with the benzyl substituent giving

Table 4. Pd-Catalyzed Carbonylation of Sulfamides **7a−d** with Aryl Halide **2m**[18]



entry		sulfamide R **8**	acyl sulfamide **9**	yield (%)[a]
1	**8a**	CH_3	**9a**	(20)[15]
2	**8a**	CH_3	**9a**	68
3	**8b**	CH_3CH_2	**9b**	47
4	**8c**	$C_6H_5CH_2$	**9c**	0

[a] Yields quoted are isolated yields.

no reaction at all (entry 4). Although we hypothesize that this may be due to steric effects, this could equally be due to a decrease in stability of the trisubstituted sulfamides and/or products under our reaction conditions.

In summary, we have developed a novel, simple, and efficient route to aryl and heteroaryl acyl sulfamides via a palladium-catalyzed carbonylation of readily available aryl or heteroaryl bromides in the presence of sulfamides. The reaction tolerates a wide range of substituted sulfamides and substituted aryl or heteroaryl halides. We anticipate that this new method will find broad application for the synthesis of a wider variety of aryl and heteroaryl acyl sulfamides than currently accessible through the known methodologies.

Acknowledgment. We are grateful to Sarah Griffiths and Richard Evans both of the Astrazeneca Charnwood Chemistry Department for their expert assistance with MS studies and microwave equipment respectively.

Supporting Information Available: Experimental procedures and full characterization (^{1}H and ^{13}C NMR data and spectra, and HRMS analysis) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100083W

(16) During the course of our work with sulfamides we have observed that they can undergo base-catalyzed thermal decomposition to release the corresponding amine. Alcaraz, L.; Bennion, C.; Morris, J.; Meghani, P.; Thom, S. M. *Org. Lett.* **2004**, *6*, 2705–2708. 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*, 202–222.

(17) Odell, L. R.; Sävmarker, J.; Larhed, M. *Tetrahedron Lett.* **2008**, *49*, 6115–6118, and references cited within.

(18) **General reaction conditions:** sulfamide **1a** (2 equiv), aryl halide (1 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ 10 mol %, triethylamine (3 equiv), DMAP (1 equiv), 0.3 M dioxane, 4 h, 100 °C, 65 psi CO.