Facile Synthesis of Acyl Sulfonamides from Carboxyic Acids using the Mukaiyama Reagent

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PII: S0040-4039(18)31471-0
DOI: https://doi.org/10.1016/j.tetlet.2018.12.030
Reference: TETL 50493

To appear in: *Tetrahedron Letters*

Received Date: 19 October 2018
Revised Date: 7 December 2018
Accepted Date: 13 December 2018

Please cite this article as: Chen, L., Luo, G., Facile Synthesis of Acyl Sulfonamides from Carboxyic Acids using the Mukaiyama Reagent, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.12.030

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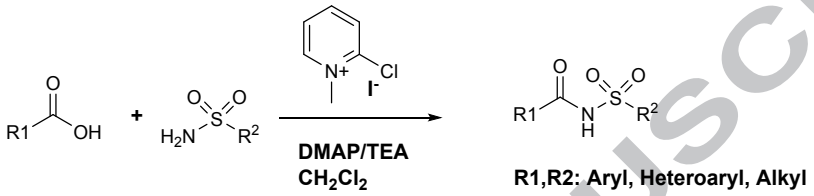

Tetrahedron Letters
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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Acyl sulfonamides
Mukaiyama reagent
Carboxylic acids coupling
Coupling with sulfonamides
Acylsulfonamides synthesis

ABSTRACT

A fast and convenient method using the Mukaiyama reagent was developed to prepare acyl sulfonamides from carboxylic acids and sulfonamides. This methodology is effective for a range of acids and sulfonamides proceeding in moderate to good yields with the majority of reactions complete within one hour under the optimized condition.

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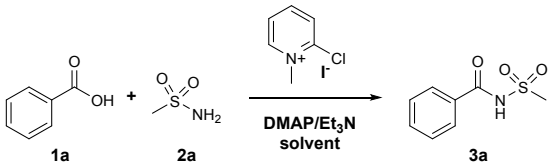
Acyl sulfonamide is an increasingly utilized motif that has been explored in many therapeutic areas of medicinal chemistry in recent years.[1] There are commonly known syntheses of acyl sulfonamides that include reacting acid chlorides/acid anhydrides with sulfonamides, the use of coupling reagents such as EDC·HCl, benzotriazole, and CDI to activate acids that react with sulfonamides in one pot.[2] However, the coupling step can be slow, often requiring an overnight reaction. Additionally, conversion from an acid to an acid chloride adds an extra step, and can be challenging if the acid substrates contain a basic amine or an acid-sensitive moiety. Another approach to the preparation of acyl sulfonamides is to employ transition metal-catalyzed carbonylation chemistry. Under microwave irradiation, various aryl and heteroaryl iodides/bromides can be carbonylated by CO released from $Mo(CO)_6$, followed by reaction of the intermediate with sulfonamides to afford the acyl sulfonamides in moderate to good yields.[3] Recently, the scope of acyl sulfonamide synthesis was expanded by reacting carboxylic acids with sulfonyl azides catalyzed by $Co_2(CO)_6$.[4] However, many sulfonyl azides are not readily available. During our research, we required an efficient method to prepare different types of acyl sulfonamides. Because of the abundance of commercially-available carboxylic acids and sulfonamides, we focused on further improving the acid/sulfonamide coupling strategy for the synthesis of acyl sulfonamides. More specifically, we were interested in employing the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide, CMPI) since it has been widely used to activate carboxylic acids to construct lactams, macrolactones and other moieties but, to the best of our knowledge, has not been used in the synthesis of acyl sulfonamides.[5] Herein, we report that CMPI is a very good coupling reagent that generally gives improved reaction yields and times, relative to some of the previously described methods, for the formation of acyl sulfonamides from various acids and sulfonamides in one pot.

Benzoic acid (**1a**) and methanesulfonamide (**1b**) were used for the model studies, as shown in Scheme 1. The initial reaction conditions used a 2:1 ratio of methanesulfonamide and benzoic acid with DMAP as a catalyst in CH_2Cl_2 (0.3 M). The suspension was stirred for 5 minutes, 2 equivalents of Et_3N were added to the reaction mixture and stirring continued at room temperature. Some heat generation was observed[6] and the suspension became clear, with precipitates appearing later. The reaction was worked up after 1 hour to give a 72% HPLC yield[7] of **3a** (Entry 1). Allowing the reaction to stir overnight improved the yield only marginally to 79%. Next, the effect of different solvents on the reaction was examined. In THF, after 1 h the reaction proceeded to ~41% conversion to the desired product while after 16 h, ~ 62% of the desired product had formed with 18% of the benzoic acid remaining, as determined by HPLC (Entry 2). The use of acetonitrile, a more polar solvent than THF, gave ~65% product with 6% benzoic acid remaining after 1 h (Entry 3). DMF behaved similarly to acetonitrile; however, more of the starting benzoic acid (~13%) remained after 1 h (Entry 4). From these screening results, CH_2Cl_2 appeared to be the best non-polar solvent while acetonitrile was the best polar solvent for conducting the coupling reaction. Since the reaction profile in CH_2Cl_2 was much cleaner than that of acetonitrile, CH_2Cl_2 was chosen as the standard solvent. By increasing the amount of Et_3N from 2 to 3 equivalents, the HPLC yield of the reaction was significantly improved to 98% in 1 hour, with a purified yield of 77% (Entry 5).[8] Because of the acidic nature of the acyl sulfonamide product, an equivalent of Et_3N may be consumed by forming a salt; thus, increasing the equivalents of the base should help to promote the overall reaction. Next the ratio of methanesulfonamide and benzoic acid was adjusted to allow for cases where the sulfonamide is expensive and would need to be the limiting reagent. Using a 1:1 ratio of methanesulfonamide and benzoic acid gave a yield of 58% by HPLC after 1 hour. Allowing the reaction mixture to stir for 16 hours afforded a 67% purified yield of the desired product (Entry 6).

Scheme 1. Method development

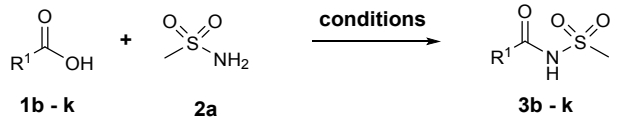


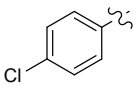
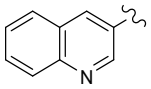
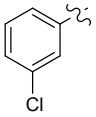
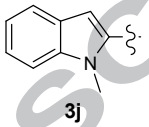
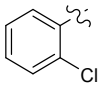
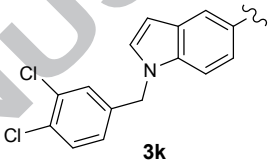
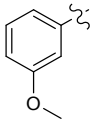
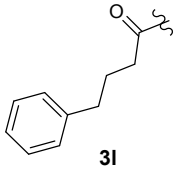
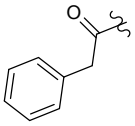
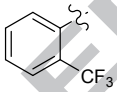
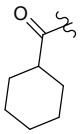
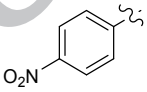
1a 2a 3a

Entry	**2**/**1** Ratio[a]	Solvent	Yield of **3** (%) 1 h (16 h)	TEA (eq)
1	2	CH_2Cl_2	72[b] (79[b])	2
2	2	THF	41[b] (62[b])	2
3	2	CH_3CN	65[b] (78[b])	2
4	2	DMF	57[b] (73[b])	2
5	2	CH_2Cl_2	98[b], (77[c])	3
6	1	CH_2Cl_2	58[b] , (67[c])	3

[a] 1.2 eq of CMPI, 0.05 eq DMAP, concentration: 0.3 M, rt; [b]HPLC yield; [c]Purified yield.

Table 1. Carboxylic acid scope



Entry	R^1	Yield (%)[a]	Entry	R^1	Yield (%)[a]
1	 **3b**	81	8	 **3i**	72
2	 **3c**	82	9	 **3j**	78
3	 **3d**	73	10	 **3k**	58[b]
4	 **3e**	89	11	 **3l**	75
5	 **3f**	91	12	 **3m**	71
6	 **3g**	78	13	 **3n**	77[c]
7	 **3h**	78	14	 **3o**	36[c]

Conditions: 1.2 eq CMPI reagent, 0.05 eq DMAP, 2.0 eq of sulfonamide, 3.0 eq of TEA, CH_2Cl_2 (0.3 M), rt.

[a] Purified yield, 1 h reaction time; [b]Purified by Prep HPLC.

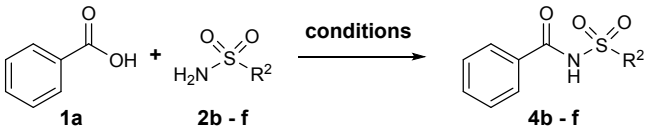
[c]Used benzenesulfonamide instead

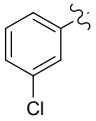
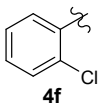
With optimized reaction conditions in hand, the scope of the carboxylic acid was explored (**1b-k**) using methanesulfonamide as the partner **2a** (Table 1). In general, this method was well tolerated for both electron-donating and electron-withdrawing groups on the benzoic acids (Entries 1-7). The reactions were often complete within 15 to 30 minutes; however, these procedures were carried out for 1 hour in the screening mode. Fused bicyclic carboxylic acids such as quinoline-3-carboxylic acid (Entry 8) and 1-methyl-indole-2-carboxylic acid (Entry 9) also participated effectively, with 72% and 78% purified yield of the desired products respectively, obtained after 1 hour. The indole analog **3k** (Entry 10) was purified by preparative HPLC and isolated in 58% yield. The primary and secondary aliphatic carboxylic acids (**3l, 3m, 3n**)

worked well with this method, while the tertiary carboxylic acid (**3o**) afforded lower but acceptable yield (36%).

The scope of the sulfonamides (**2b –f**) with benzoic acid **1a** was explored next (Table 2). Simple aliphatic sulfonamides (Entry 1, 2) behaved similarly as methanesulfonamide with good isolated yields. Gratifyingly, aromatic sulfonamides (Entry 3 - 5) also coupled well to give good yields of the desired products.

Table 2. Sulfonamide scope

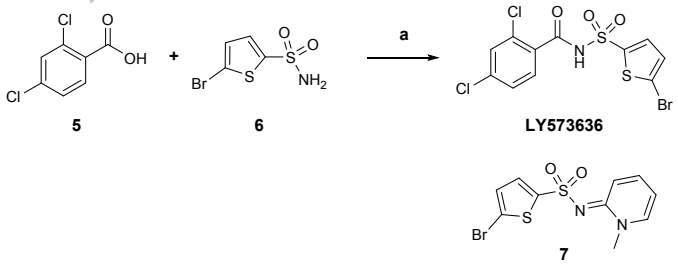


Entry	R^2	Yield (%)[a]	Entry	R^2	Yield (%)[a]
1	 **4b**	83	4	 **4e**	84
2	 **4c**	89	5	 **4f**	87
3	 **4d**	83			

[a]Isolated yield, 1 h.

To demonstrate the utility of this method, LY573636, an antitumor agent that possesses an acyl sulfonamide moiety, was prepared by this method (Scheme 2). LY573636 was obtained in 65% yield (0.6 mmol scale) using the standard reaction conditions.[9] When conducted on a 6 mmol scale, LY573636 was obtained 76% yield after 1 hour of stirring. Interestingly, **7** was isolated as a by-product in 15% yield, believed to have arisen from the CMPI reagent reacting with the sulfonamide (Scheme 3). In the small scale screening reactions only a few of the couplings showed a small amount of the corresponding sulfonamide adduct.[10]

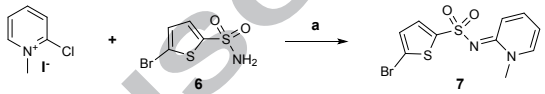
Scheme 2. Synthesis of **LY573636**



a: 1.2 eq CMPI, 0.05 eq DMAP, 3.0 eq of TEA, CH_2Cl_2 (0.3 M), rt.

In order to investigate the reaction kinetics, an experiment was carried out in absence of the acid coupling partner. In this experiment it was shown that the CMPI reagent reacted with sulfonamide **6** over 1 hour to form **7** with 77% conversion (Scheme 3). Subsequent addition of acid **5** to the reaction mixture did not result in the formation of the acyl sulfonamide product, suggestive of a competitive reaction between the acid and the sulfonamide with CMPI.[11] Interestingly, the carboxylic acids are activated significantly faster by the CMPI reagent than are the sulfonamides, which presumably allows for good conversion to the acyl sulfonamide product with little to no pyridin-2(1*H*)-ylidene)methanesulfonamide-derived side products.

Scheme 3. Reaction of sulfonamide **6** with the Mukaiyama reagent



a: 1.0 mmol CMPI, 1.7 mmol of **6**, 0.04 mmol DMAP, 2.5 mmol of TEA, DCM (0.3 M), rt.

In conclusion, we have described the development of a quick and efficient preparative procedure to access acyl sulfonamide derivatives from carboxylic acids using the CMPI reagent. An excess of sulfonamide (2.0 eq) can be used to drive the reaction to completion within 1 hour of stirring at room temperature in most cases. When the sulfonamide is the limiting reagent, a 1:1 ratio of carboxylic acid to sulfonamide can be used in conjunction with a longer reaction time to obtain satisfactory yields. This method is also amenable to large scale synthesis. We were able to routinely utilize this facile synthesis of acyl sulfonamides in a drug discovery program focused on the preparation of $Na_v1.7$ inhibitors that allowed an expedient expansion the SARs in a series of analogs.[12]

Acknowledgments

We gratefully acknowledge Drs. Carolyn Dzierba and Nicholas Meanwell for careful reading of this manuscript and Robert Langish, Linping Wang for HRMS analysis .

References and Notes

1. (a) Bowsher, M.; Hiebert, S.; Li, R.; Wang, A. X.; Friborg, J.; Yu, F.; Hernandez, D.; Wang, Y-K.; Klei, H; Rajamani, R.; Mosure, K; Knipe, J. O.; Meanwell, N. A.; McPhee, F.; Scola, P. M. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 43. (b) Sun, L.Q.; Mull, E.; Zheng, B.; D'Andrea, S.; Zhao, Q.; Wang, A. X.; Sin, N.; Venables, B. L.; Sit, S-Y.; Chen, Y.; Chen, J.; Cocuzza, A.; Bilder, D. M.; Mathur, A.; Rampulla, R.; Chen, B.C.; Palani, T.; Ganesan, S.; Arunachalam, P.N.; Falk, P.; Levine, S.; Chen, C.; Friborg, J.; Yu, F.; Hernandez, D.; Sheaffer, A.K.; Knipe, J.O.; Han, Y. H.; Schartman, R.; Donoso, M.; Mosure, K.; Sinz, M. W.; Zvyaga, T.; Rajamani, R.; Kish, K.; Tredup, J.; Klei, H. E.; Gao, Q.; Ng, A.; Mueller, L.; Grasela, D. M.; Adams, S.; Loy, J.; Levesque, P. C.; Sun, H.; Shi, H.; Sun, L.; Warner, W.; Li, D.; Zhu, J.; Wang, Y. K.; Fang, H.; Cockett, M. I.; Meanwell, N. A.; McPhee, F.; Scola, P. M. *J. Med. Chem.* **2016**, *59*, 8042; (c) Ammazzalorso, A.; De Filippis, B.; Giampietro, L.; Amoroso, R.; *Chem. Biol. Drug Des*. **2017**, *90*, 1094; (d) DiMauro, E. F.; Altmann, S.; Berry, L. M.,; Bregman, H.; Chakka, N.; Chu-Moyer, M.; Bojic, E. F.; Foti, R. S.; Fremeau, R.; Gao, H.; Gunaydin, H.; Guzman-Perez, A.; Hall, B. E.; Huang, H.; Jarosh, M.; Kornecook, T.; Lee, J.; Ligutti, J.; Liu, D.; Moyer, B. D.; Ortuno, D.; Rose, P. E.; Schenkel, L. B.; Taborn, K.; Wang, J.; Wang, Y.; Yu, V.; Weiss, M. M. *J. Med. Chem.* **2016**, *59*, 7818.

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6. The observed temperature increase when addition of TEA to the reaction mixture was probably due to the heat generation of combination of TEA reacting with acid and acid activation with CMPI together. The reaction of the activated acid with sulfonamide seems did not contribute to the heat generation. More details can be found in the supporting information..
7. HPLC yield was roughly estimated with the integration of benzoic acid, the product and the possible activated acid intermediate. More details can be found in the supporting information.
8. LCMS showed that the aqueous layer contained some of the product. The yield could be higher if multiple back extractions of the aqueous layer with ethyl acetate were to be performed.
9. Procedure: DCM (2.0 mL) was added to a 20 mL vial containing DMAP (3.81 mg, 0.031 mmol), 2-chloro-1-methylpyridin-1-ium iodide (0.191 g, 0.748 mmol), 2,4-dichlorobenzoic acid (0.119 g, 0.623 mmol), 5-bromothiophene-2-sulfonamide (0.302 g, 1.25 mmol) at rt. After stirring for 5 min, TEA (0.261 ml, 1.869 mmol) was slowly added to the reaction mixture. The reaction was stirred at rt for 1 h. The reaction solvent was concentrated under vacuum and the crude residue was taken up in ethyl acetate, washed with 1N HCl (1 mL), water, and brine. The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated. The crude material was purified by silica gel flash column chromatography eluting with ethyl acetate in hexane from 0 to 30% to give the desired product (0.168 g, 65%) as colorless crystals: ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.73 (d, *J* = 4.1 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.36 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.14 (d, *J* = 4.1 Hz, 1H).
10. For example, in Entry 1 of Table 2 we found the corresponding side product (~5% by LCMS) mixed in with the desired product after purification by flash silica gel chromatography.
11. 5 was 0.85 mmol so in the end the ratio of this reaction condition was the optimal condition.
12. (a) Luo, G.; Chen, L.; Easton, A.; Newton, A.; Bourin, C.; Shields, E.; Mosure, K.; Soars, M.; Knox, R.; Matchett, M.; Pieschl, R.; Post-Munson, D.; Wang, S.;. Herrington, J.; Graef, J.; Newberry, K.; Sivarao, D.; Senapati, A.; Bristow, L.; Meanwell, N.A.; Thompson, L.; Dzierba, C. *Manuscript submitted.* (b) Wu, Y-J.; Venables, B.; Guernon, J.; Chen, J.; Sit, S.; Rajamani, R.; Knox, R.; Matchett, M.; Pieschl, R.; Herrington, J.; Bristow, L.; Meanwell, N.; Thompson, L.; Dzierba, C. *Manuscript submitted.*

Supplementary Material

^{1}H NMR and LCMS of compounds in Method Development, Table 1, Table 2, and Scheme 2.

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Graphical Abstract

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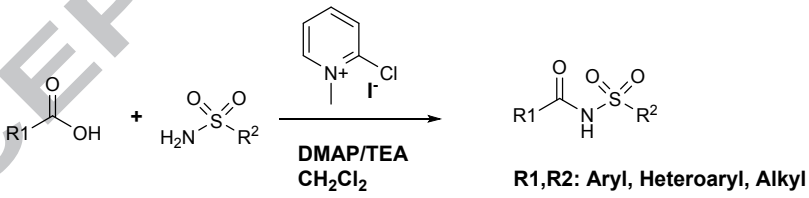

- Acylsulfonamides were synthesized within 1 hour using Mukaiyama reagent(CMPI)/DMAP/TEA method at optimal condition.
- Method was efficient with broad scope of aryl/heteroaryl and alphatic caboxylic acids.
- Method tolerated various aliphatic, aryl and heteroaryl sulfonamides.
- Method was simple to operate at room temperature under atmosphere condition.