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One-pot synthesis of sulfamoylguanidines and sulfonylguanidines

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Abstract

N,*N*-Disubstituted sulfamoylguanidines and sulfonylguanidines can be synthesized from sulfamide or sulfonamides and isothiocyanates in two very efficient one-pot procedures. © 2000 Published by Elsevier Science Ltd.

Sulfamoylguanidine and sulfonylguanidine derivatives are of general interest since they exhibit a broad range of biological activities.[1–3] They are structural equivalents of urea but with an extra site (R group in **3**) that can be derivatized. Typically, the synthesis of sulfamoylguanidines involves the stepwise or simultaneous replacement of both phenoxy groups of diphenyl *N*-sulfamoylcarbonimidate,[4] or both methylthio groups of dimethylthio *N*-sulfamoylcarbonimidate[3] by nucleophilic amines. However, the displacement of the second phenoxy group or methylthio group requires more forceful conditions, especially when less nucleophilic amines are used. While the synthesis of sulfonylguanidines has received considerable attention,[5] a convenient one-pot synthesis from sulfonamides is still lacking.

We wish to report two very efficient procedures for the synthesis of sulfamoylguanidines and sulfonylguanidines from readily available sulfamide and sulfonamides, respectively. Analogous to the synthesis of cyanoguanidines from sodium cyanamide and isothiocyanates,[6] we envisioned that the intermediate sulfamoylthiourea anion **2** generated by the reaction of sodium sulfamide with an isothiocyanate would provide sulfamoylguanidine **3** by the action of a thiocarbonyl activating reagent and a requisite amine (Scheme 1).

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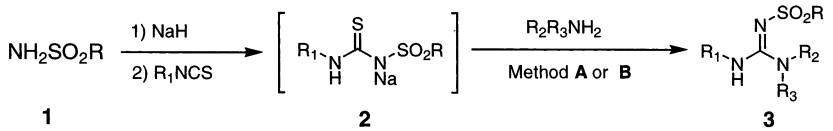
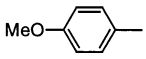
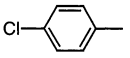


Entry	R	R_1	R_2	R_3	Method*	Yield of **3** (%)**
a	NH_2		*n*-Bu	H	A	90
					B	85
b	NH_2		*t*-Bu	H	A	87
					B	75
c	NH_2		*i*-Pr	*i*-Pr	A	85
					B	80
d	NH_2		Ph	H	A	75
					B	86
e	NH_2		*n*-Bu	H	A	70
					B	77
f	NH_2	$PhCH_2CH_2$	*n*-Bu	H	A	81
					B	80
g	NMe_2		*n*-Bu	H	A	85
					B	85
h	Me		*n*-Bu	H	A	90
					B	92
i	Ph		*n*-Bu	H	A	90
					B	90

*A: mercury (II) chloride; B: 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrchloride. ** All compounds were purified by column chromatography and characterized by ^1H NMR, ^{13}C NMR and MS analysis.

Scheme 1.

Although the reaction between sodium sulfamide and phenyl isothiocyanate is slow at room temperature (6 h, 95% conversion), the reaction was complete in 30 min at 60°C in DMF. The formation of intermediate **2a** can be monitored by LC–MS or TLC analysis which showed quantitative conversion of the starting phenylisothiocyanate to the more polar **2a**.[7] Since 2-chloro-1-methylpyridinium iodide (**4**) (Mukaiyama's reagent[8]) has been demonstrated to be able to convert thioureas into carbodiimides, the intermediate **2a** was subjected to reaction with **4** in the presence of *n*-butylamine. Only 31% of sulfamoylguanidine **3a** was isolated after 24 h at room temperature, with the majority of **2a** remaining unchanged even after heating for an extended period of time. Encouraged by this result, we replaced reagent **4** with mercury(II)

chloride, a reagent known to generate bis-BOC-carbodiimide (or its mercury complex) from *N*,*N*′-di-(*tert*-butoxycarbonyl) thiourea.[9] To our satisfaction, sulfamoylguanidine **3a** was isolated in 90% yield after stirring for 10 min at room temperature (Method A).

We were also inspired by the report by Atwal[6] that a cyanothiourea was converted into the cyanoguanidine by the action of a requisite amine in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI). We found that it was also applicable to the synthesis of sulfamoyl guanidines. Indeed, the intermediate **2a** was reacted with *n*-butylamine and EDCI in the same pot to give product **3a** in 85% isolated yield after 3 h at room temperature (Method B).

To investigate the scope and limitations of these methods, we have prepared several additional compounds from a range of structurally different isothiocyanates and amines. As shown in the Table,[10] both aryl and alkylisothiocyanates are allowed in these reactions (entry a and f), as is the presence of a substituent on the aromatic ring (entry d and e). The results with hindered amines are equally satisfactory (entry b and c). When less nucleophilic aniline was used, di-aryl substituted sulfamoylguanidine was obtained in high yield (entry d). These methods are not only limited to sulfamoylguanidines as sulfonylguanidines can also be prepared under similar condition (entry h and i).[11]

In conclusion, we have developed two one-pot procedures (Method A and B) for the synthesis of sulfamoylguanidines and sulfonylguanidines from sulfamide and sulfonamides, respectively. Both routes proceed efficiently under mild conditions and provide excellent yields of products.

Acknowledgements

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5. For sulfonylguanidine synthesis methods, see: Deprez, P.; Vevert, J.-P. *Synth. Commun.* **1996**, 4299.
6. Atwal, K.; Ahmed, S. Z.; O'Reilly, B. C. *Tetrahedron Lett.* **1989**, *30*, 7313.
7. ^{1}H NMR (DMSO) for **2a** (quenched with H_2O): 9.68 (s, 1H), 7.74–7.16 (m, 5H), 3.36 (s, 3H).
8. (a) Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 575. (b) Yong, Y. F.; Kowalski, J. A.; Lipton. M. A. *J. Org. Chem.* **1977**, *62*, 1540.
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10. Typical procedures: to a solution of sulfamide (42 mg, 0.44 mmol) in dimethylformamide (1 mL) was added sodium hydride (95%, 11 mg, 0.44 mmol). After stirring for 5 min, phenyl isothiocyanate (48 μL, 0.4 mmol) was added via a syringe. The reaction was stirred at 60°C for 30 min (or at room temperature for 7 h), upon which time TLC indicated complete conversion of phenyl isothiocyanate to **2a**. **Method A**: to the above mixture was

added *n*-butylamine (44 μL, 0.44 mmol) and mercury(II) chloride (119 mg, 0.44 mmol). After stirring at room temperature for 10 min, the reaction was diluted with ethyl acetate (10 mL) and filtered through a pad of celite. Purification on silica gel column gave 97 mg of **3a** (90% yield). **Method B**: to the above mixture was added *n*-butylamine (44 μL, 0.44 mmol) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (85 mg, 0.44 mmol). After stirring at room temperature for 3 h, the reaction was quenched with water and extracted with ethyl acetate (3×5 mL). The organic phase was washed with saturated sodium chloride solution, dried over magnesium sulfate and filtered. The solvent was removed to give the crude product. Chromatography on silica gel with 5–10% MeOH in EtOAc provided **3a** as a colorless oil (92 mg, 85% yield). Spectral data for **3a**: ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.43 (t, 2H, $J=7.5$ Hz), 7.33–7.27 (m, 1H), 7.23 (d, 2H, $J=7.5$ Hz), 4.80 (s, 3H), 3.31–3.26 (m, 2H), 1.50–1.40 (m, 2H), 1.35–1.20 (m, 2H), 0.89 (t, 3H, $J=6.8$ Hz); ^{13}C NMR: ($CDCl_3$): δ 153.99, 135.41, 130.07, 127.45, 125.89, 41.28, 31.23, 19.86, 13.64. HRMS for $C_{11}H_{18}N_4O_2S$, calcd for $(M+H)^+$: 271.1228, found: 271.1233.

11. The reactions of sodium salt of sulfonamides (entry h and i) with phenyl isothiocyanate are complete within 30 min at room temperature.