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One-pot synthesis of *N*,*N*′-disubstituted acylguanidines

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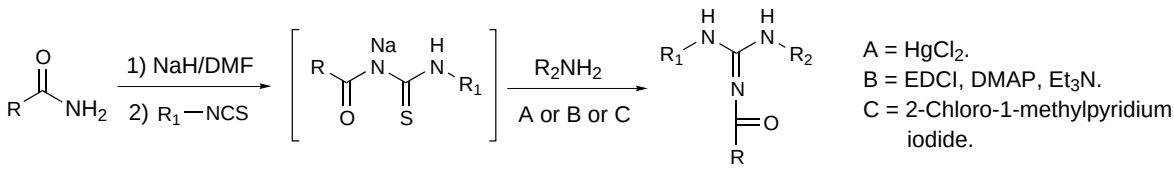
Abstract—Acylguanidines are isosteres of thioureas (or ureas) and are possible prodrugs of guanidines. A convenient one-pot synthesis of *N*,*N*′-disubstituted acylguanidines from primary amides is described.

We recently required an efficient method for the synthesis of acylguanidines as surrogates of thioureas and cyanoguanidines. Classically, *N*,*N*′-disubstituted acylguanidines are prepared by the reaction of *N*,*N*′-disubstituted guanidines with various acylating agents.[1] However, this procedure usually leads to a mixture of mono- and multi-acylation products. Alternative methods involve the stepwise or simultaneous replacement of both methylthio groups of dimethylthio-*N*-acylcarbonimidate by nucleophilic amines[2] or the ring-opening reaction of 2-acylimino-1,3-thiazetdines.[3] All of these methods require the availability of necessary starting materials, which are often difficulty to obtain or involve high temperature and the generation of noxious mercaptans. More recently, several reports[4] have demonstrated that an acylthiourea can be converted to corresponding acylguanidine by the EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) coupling reaction with an amine.

In a previous paper,[5] we reported two one-pot procedures for the synthesis of *N*,*N*′-disubstituted sulfamoylguanidines and sulfonylguanidines from sulfamides and sulfonamides, respectively. Both routes proceed efficiently under mild conditions and provide excellent yields of products. In this report, we disclose the synthesis of acylguanidines from primary amides.

Analogous to the synthesis of sulfamoylguanidines[5] and cyanoguanidines,[6] we envisioned that the intermediate acylthiourea anion **2a**, generated by the reaction of a primary amide anion with an isothiocyanate, would provide a *N*,*N*′-disubstituted acylguanidine by the action of a thiocarbonyl activating reagent and a requisite amine (Scheme 1).[7] Intermediate **2a** (R_1 = phenyl) was synthesized from benzamide anion and phenyl isothiocyanate. The formation of intermediate **2a** can be monitored by LC-MS or TLC analysis, which showed total conversion of the starting phenyl isothiocyanate to **2a** in 30 min at 60°C. After cooling to room temperature, the reaction mixture was treated with *n*-butylamine and mercury(II) chloride[8] to provide *N*-phenyl-*N*′-*n*-butyl benzoyl guanidine **3a** in 73% yield. As expected, we also found that EDCI and 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent[9]) are also capable of converting intermediate **2a** to *N*-benzoylguanidine **3a** in comparable yields (entry a).

To investigate the scope and limitations of these methods, we have prepared several additional compounds from a range of structurally different amides and isothiocyanates. Since all three procedures gave comparable yields, only method B was utilized to carry out the additional studies. As shown in Table 1, both alkylacylguanidines (entry b) and benzoylguanidines can be



Scheme 1.

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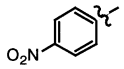
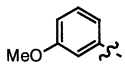
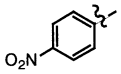
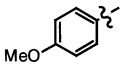
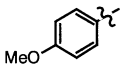
Table 1.

Entry	R	R_1	R_2	Method[a]	Yield of **3** (%)[b]
a			*n*-Bu	A	73
				B	78
				C	75
b	*n*-Pr		*n*-Bu	B	50
c			*n*-Bu	B	59
d			*n*-Bu	B	80
e			*n*-Bu	B	30
f			*n*-Bu	B	74
g			*t*-Bu	B	69
h				B	61
i			*n*-Bu	B	55

[a]A: mercury (II) chloride; B: EDCI; C: 2-chloro-1-methylpyridinium iodide. [b]All compounds were purified by silica gel column chromatography and characterized by ^{1}H NMR, ^{13}C NMR and MS analysis. All yields are isolated yields and are the average of at least of two runs.

synthesized by these methods. The electron-withdrawing (entry c) and electron-donating (entry d) substitutions on the benzamide are allowed in these reactions, as is the heterocyclic ring (entry i). Similarly, phenyl isothiocyanates can tolerate both electron-withdrawing (entry e) and electron-donating (entry f) substituents. The yield is lower when 4-nitrophenylisothiocyanate is used as a starting material; *N*-*n*-butyl benzamide is obtained as a side product. Both hindered amines (entry g) and anilines (entry h) participate in the reaction to give satisfactory yields.

In conclusion, we have developed three one-pot procedures (Methods A, B and C) for the synthesis of *N*,*N*′-disubstituted acylguanidines from primary amides and isothiocyanates. The reaction proceeds under mild conditions and provides excellent yields of *N*,*N*′-disubstituted acylguanidines.

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7. Typical procedures. Typical experiment: To a solution of benzamide (29 mg, 0.24 mmol) in dimethylformamide (0.5 mL) was added sodium hydride (95%, 7.2 mg, 0.31 mmol). After stirring for 5 min, phenyl isothiocyanate (24 μL, 0.20 mmol) was added via a syringe. The reaction was stirred at 60°C for 30 min, upon which time TLC indicated complete conversion of phenyl isothiocyanate to **2a**. **Method A**: To the above mixture was added *n*-butylamine (24 μL, 0.24 mmol) and mercury(II) chloride (65 mg, 0.24 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, and the filtrate was concentrated. Purification of the residue on a silica gel column gave 43.6 mg of **3a** (73% yield). **Method B**: To the reaction mixture (**2a**) was added *n*-butylamine (24 μL, 0.24 mmol) and EDCI (46 mg, 0.24 mmol) and a catalytic amount of 4-dimethylaminopyridine. 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 a saturated sodium chloride aqueous solution and dried over magnesium sulfate. The solvent was removed to give a crude product. Purification of the crude product on a silica gel column with 5–10% MeOH in EtOAc provided **3a** (46.5 mg, 78% yield). **Method C**: To the reaction mixture (**2a**) was added *n*-butylamine (24 μL, 0.24 mmol) and 2-chloro-1-methylpyridinium iodide (61.3 mg, 0.24 mmol) and triethylamine (33 μL, 0.24 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. Purification of the crude product on a silica gel column with 5–10% MeOH in EtOAc provided **3a** (45.1 mg, 75% yield). Spectral data for **3a**: ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 2H, $J=7.4$ Hz), 7.63 (t, 1H, $J=7.5$ Hz), 7.50 (t, 2H, $J=7.5$ Hz), 7.45 (t, 2H, $J=7.6$ Hz), 7.37 (t, 1H, $J=7.0$ Hz), 7.30 (d, 2H, $J=7.5$ Hz), 2.87 (m, 2H), 1.52 (m, 2H), 1.23 (m, 2H), 0.82 (t, 3H, $J=7.5$ Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 171.26, 163.52, 163.14, 153.57, 135.05, 134.36, 130.89, 129.74, 128.97, 128.85, 127.87, 124.72, 77.32, 77.00, 76.67, 44.98, 30.81, 19.51, 13.26 ppm; HRMS for $C_{18}H_{21}N_3O$, calcd for $(M+H)^+$: 296.1763, found: 296.1776.

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