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An Efficient Method for the Preparation of Amidinoureas

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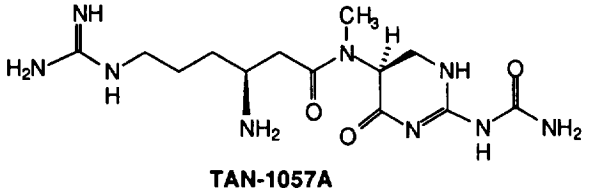
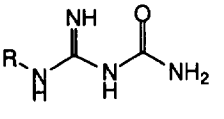
Abstract. A mild and efficient method for the preparation of amidinoureas by reaction of an acyl-S-methylisothiourea with an amine followed by removal of the acyl groups is described.

We recently required a mild and efficient method for the preparation of amidinoureas from peptide amine residues. This unusual structural array is part of the recently discovered anti-MRSA peptide antibiotics TAN-1057A. [1] All the existing methods, which includes the reaction of guanidines with isocyanates, [2] hydrogenation of 5-amino-3-amino-1,2,4-oxadiazoles,[3] or the hydrolysis of cyanoguanidines under strongly acidic condition [4] are either, inefficient, involve harsh reaction conditions, or require numerous steps. We have found that none of these methods are suitable for accessing the labile TAN-1057 amidinourea substructure.



TAN-1057A

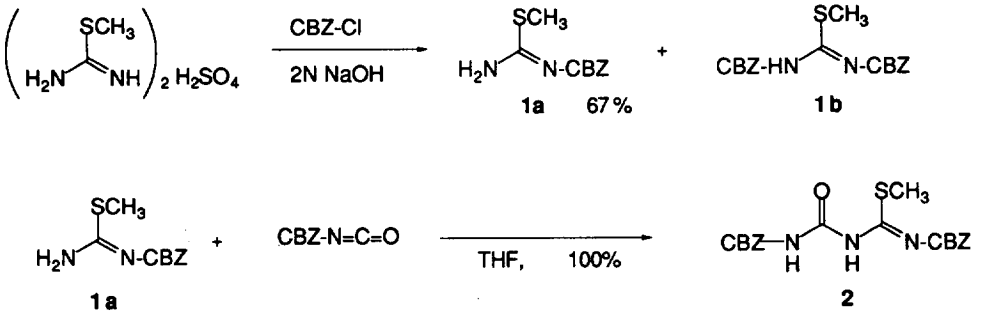


AMIDINOUREA

The efficient synthesis of guanidines via reaction of acyl-S-methylisothioureas [5] with amines in weakly basic media prompted us to explore the preparation of aminidoureas from acylureido-S-methylisothioureas. It was reasoned that selection of a suitable acyl protecting group, such as N-CBz, would allow for the direct preparation of amidinoureas that would be compatible with peptide synthesis strategies. Herein, we wish to report a general and mild method to prepare amidinoureas from primary and secondary amines.

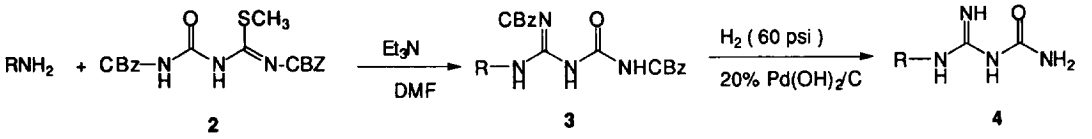
As shown in Scheme 1, N-(benzyloxycarbonyl)ureido-N'-benzyloxycarbonyl-S-methylisothiourea **2** [6] was prepared from mono-benzyloxycarbonyl-S-methylisothiourea **1a** and benzyloxycarbonylisocyanate [7] (THF, 100%). Mono-benzyloxycarbonyl-S-methylisothiourea **1a** was readily obtained by the slow addition of one equivalent of a solution of benzylchloroformate in CH_2Cl_2 to a cold mixture of S-methylisothiourea semisulfate in CH_2Cl_2/ 2N NaOH.[5c] The bis-acylated product, N,N'-

bis(benzyloxycarbonyl)-S-methylisothiourea **1b** was also produced, but can be easily separated from **1a** by silica gel column chromatography.



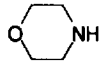
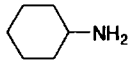
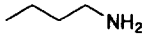
SCHEME 1

When N-(benzyloxycarbonyl)ureido-N'-benzyloxycarbonyl-S-methylisothiourea (**2**) was condensed with amines **a-d** (Scheme 2, Table 1) in the presence of triethylamine in DMF with stirring at room temperature, the N^G, N^U-bis(benzyloxycarbonyl)-amidinoureas (**3a-d**) were produced in good yield. Removal of the N-CBz group was achieved by hydrogenation (H_2 / 20% $Pd(OH)_2$ on carbon) to provide the amidinoureas **4 a-d** in excellent yields.

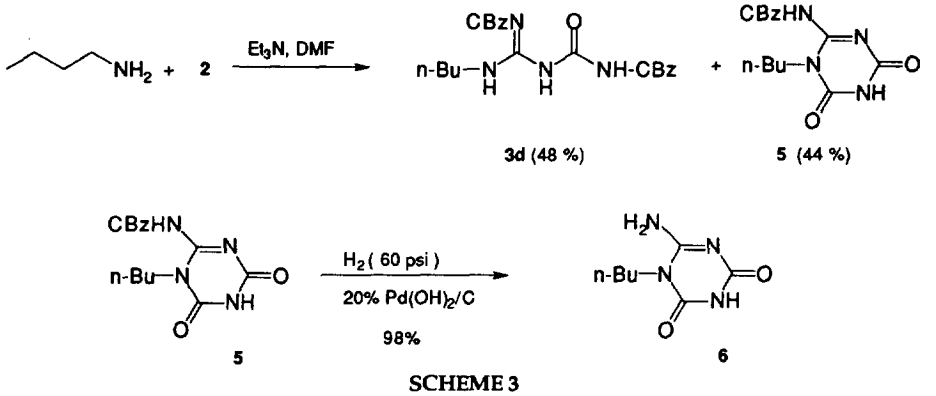


SCHEME 2

Table 1

Entry	Amines	Yield of 3	Yield of 4	Ref.
a		81 %	96 %	3
b		75 %	97%	
c		99 %	93 %	11
d		48 %	99%	3

An interesting observation was made in the case of n-butylamine (entry **d**). Under the same reaction conditions as those employed for the other substrates, this substrate produced about a 1:1 ratio of the expected product **3d** and a cyclic by-product, triazine **5** (Scheme 3).[9] If the reaction was allowed to proceed longer (12 hours instead of 4 hours), the trazine **5** was the only product isolated. It is believed that the initially formed **3d** cyclizes to the triazine in the presence of excess triethylamine to form more the stable 1,3,5-triazine-2,4-dione. The formation of the triazine by-product is, of course, precluded from the secondary amines (entry **a** and **b**) and the more sterically hindered cyclohexylamine (entry **c**) does not readily cyclize to this system. The N-CBz group of the protected triazine **5** can be simply removed by catalytic hydrogenation to give 2-amino-1-n-butyl-4,6-dioxo-tetrahydro-*s*-triazine **6**.[8,10]



SCHEME 3

Typical experimental procedure: To a mixture of **2** (401 mg, 1.0 mmole, 1.0 eq.) in DMF (9 mL) was added morpholine (131 mg, 1.5 mmole, 1.5 eq.) and triethylamine (303 mg, 3.0 mmole, 3.0 eq.). The resulting mixture was stirred overnight at room temperature. The reaction mixture was poured into CH_2Cl_2. The organic layer was washed with 1N HCl, sat. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and separated by column chromatography on silica gel (eluted with CH_2Cl_2:ethyl acetate: MeOH , 75:20:5) to afford 332 mg (75 % yield) of **3b** as a white solid. ^{1}HNMR (300MHZ, $CDCl_3$ vs TMS) δ 3.59 (4H, m), 3.71 (4H, m), 5.14 (2H, s), 5.20 (2H, s), 7.36 (10H, m), 7.75 (1H, br., D_2O exch.), 11.43 (1H, br., D2O exch.). IR (NaCl, film) 3244, 2963, 1731, 1652 1605, 1472, 1361, 1288, 1252, 1217, 1186, 1111, 1026 cm^{-1}; mp 121-2 ^oC (recryst. MeOH / CH_2Cl_2 / EtOAc); Anal. calcd. for $C_{22}H_{24}N_4O_6$: C, 59.99, H, 5.49, N, 12.72; Found: C, 60.02; H,5.49; N, 12.70.

To a solution of **3b** (277 mg, 0.63 mmol, 1.0 eq.) in MeOH (3 mL)/ THF (6 mL) was added 20% $Pd(OH)_2/C$ (30 mg). The reaction vessel was charged with H_2 and the mixture was hydrogenated at 60 psi for 24h. The mixture was then purged with nitrogen, and filtered to remove the catalyst. The filtrate was concentrated and dried *in vacuo*. to give 105 mg (97% yield) of product **4b** as a semi-solid.: ^{1}HNMR (300MHZ, CD_3OD) δ 3.51 (4H, t., J=5.0 Hz), 3.68 (4H, t., J=5.1 Hz) ppm; ^{13}CNMR (75 MHZ, CD_3OD) δ 46.56, 67.58, 161.5, 168.7 ppm. IR (NaCl, film) 3459, 3359, 2966, 2865, 1644, 1600, 1566, 1513, 1397, 1369, 1273, 1117, 1002 cm^{-1}. Anal. calcd. for $C_6H_{12}N_4O_2$: C, 41.85, H, 7.02, N, 32.54; Found: C, 41.75; H, 6.85; N, 32.23.

The current methodology provides a mild and efficient means to prepare acylamidinoureas and amidinoureas from simple amines. Application of this methodology to the preparation of TAN-1057A and related substances will be reported on in due course.

Acknowledgment. We are indebted to the National Science Foundation (CHE 8717017) and Microcide Pharmaceutical Co. for providing financial support. Mass spectra were obtained on instruments supported by the National Institutes of Health Shared Instrumentation Grant GM49631.

References and Footnotes

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6. Data for **2**: ^{1}HNMR (300MHZ, DMSO-d_6 vs TMS) δ 2.29 (3H, s), 5.15 (2H, s), 5.22 (2H, s), 7.40 (10H, m) ppm. IR (NaCl, film) 3226, 3159, 2925, 1749, 1715, 1558, 1469, 1261, 1205 cm^{-1}. mp 165-6 °C (recryst. CH_2Cl_2 / EtOAc). Anal. calcd. for $C_{10}H_{12}N_2O_2S$: C, 56.85, H, 4.77, N, 10.47, S 7.99; Found: C, 57.00; H,4.97; N, 10.36; S, 7.76.

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9. Data for **5**: ^{1}HNMR (300MHZ, $CDCl_3$ vs TMS) δ 0.93 (3H, t, J =7.34 Hz), 1.35 (2H, m), 1.63 (2H, m), 4.00 (2H, t, J = 7.8 Hz), 5.21 (2H, s), 7.83 (5H, m), 9.18 (1H, D_2O exch.), 11.86 (1H, D_2O exch.) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 13.83, 19.96, 29.54, 42.93, 68.42, 128.53, 128.59 (2C), 128.69 (2C), 135.74, 146.26, 148.96, 152.91, 163.18 ppm. IR (NaCl, film) 3216, 3106, 296, 1730, 1654, 1608, 1467, 1379, 1318, 1242, 1169, 1083 cm^{-1}. mp 139 °C (decomp.) (recryst. CH_2Cl_2 / EtOAc); HRMS (FAB) calcd. for $C_{15}H_{19}N_4O_4$: (M+H) 319.1406; Found: 319.1408.

10. Data for **6**: ^{1}HNMR (300MHZ, CD_3OD) δ 0.99 (3H, t, J =7.50 Hz), 1.41 (2H, m), 1.64 (2H, m), 3.87 (2H, t, J = 6.90 Hz) ppm; ^{13}CNMR (75 MHZ, $CDCl_3$) δ 13.69, 19.13, 29.16, 41.25, 150.2, 153.0, 156.4 ppm. IR (NaCl, film) 3353, 3186, 3089, 2957, 1744, 1644, 1548, 1514, 1416, 1023 cm^{-1}. mp > 250 °C . HRMS (FAB) calcd. for $C_7H_{13}N_4O_2$ (M+H): 185.1039; Found: 185.1041.

11. Data for **4c**: ^{1}HNMR (300MHZ, CD_3OD) δ 1.38 (5H, m), 1.62 (1H, m), 1.75 (2H, m), 1.93 (2H, m), 4.53 (1H, m) ppm. ^{13}CNMR (75 MHZ, CD_3OD) δ 25.51, 26.24, 33.31, 51.22, 156.8, 171.2 ppm. IR (NaCl, film) 3326, 2934, 2858,1717, 1682, 1614, 1453, 1416, 1345, 1152, 1102, 1046 cm^{-1}. HRMS: calcd. for $C_8H_{16}N_4O$ (M+ H): 185. 1402; Found: 185.1408.

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