

SYNTHESIS OF DIACYLAMINES AND THE PREPARATION OF α -AMINO-ACYLUREAS, A NEW TYPE OF α -AMINO ACID DERIVATIVES

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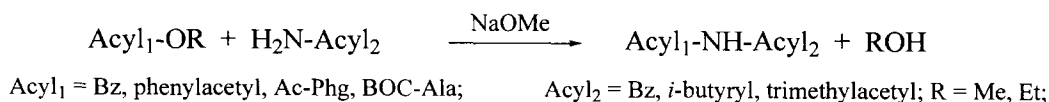
Received 24 June 1998; accepted 31 August 1998

Abstract: Sixteen new and one known unsymmetrical open-chain diacylamines were synthesized by sodium methoxide catalyzed acylation of amides with carboxylic esters and acylamino-carboxylic esters, or acylureas with acylamino-carboxylic esters and α -amino acid esters. © 1998 Elsevier Science Ltd. All rights reserved.

We describe a straightforward synthesis of open chain diacylamines, $R_1CO-NH-CO-R_2$ (acyclic imides), including the first synthesis of α -amino-acylureas of the $H_2N-CHR-CO-NH-CO-NH_2(R')$ type. In the context of this work, acylureas (ureides) are considered diacylamines of carboxylic acids and carbamic acids, with the $-CO-NH-CO-$ group as the common core constituent.

Diacylamines are used in peptide syntheses as acylating compounds.¹ Both diacylamine moieties of thalidomide acylate proteins, nucleic acids and other cell constituents in vivo.^{2,3} While cyclic diacylamine moieties occur in many antineoplastic drugs (dihydrofluorouracil, dioxopiperazines, naphtalimides, etc.) and antiepileptics (hydantoines, succinimides, barbiturates etc.), there are only few related compounds containing open chain diacylamine moieties, for example, derivatives of the N-benzoyl-N'-phenylurea^{4,5} and haloacetamino-benzoylureas⁶ with antineoplastic activity, and the antiepileptic phenylacetylurea and its derivatives.⁷

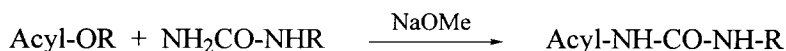
Available synthetic methods for open chain diacylamines involve prolonged reaction times and/or other experimental inconveniences.^{8–10} The present technique is based on the sodium alkoxide catalyzed barbiturate synthesis.¹¹ We have prepared 17 diacylamines, 16 hitherto unreported (**1**, **2**, **4–17**) and one known⁸ (**3**), by acylation primary amides with carboxylic esters in the presence of Na methoxide in vacuum (to remove ROH), at 25 °C for 30 min (Scheme 1). Note that this type of reaction at high (>50 °C) temperature, and in the presence of alcohol, may yield mixtures of products with exchanged amide and ester functions of the starting materials.¹²



Scheme 1

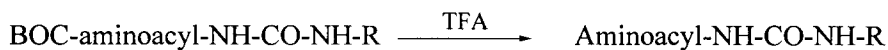
The reaction proceeds easily with carboxylic esters, esters of acylamino acids, and amino acid esters with carboxylic group attached to primary or secondary carbon atom, but it fails with trimethylacetic acid ester or urethane as acylating agent. The primary amide groups of urea or substituted ureas could be acylated using the same conditions.

Diacylamines of amino acids and carbamic acids, **12–15**, were prepared by acylation of urea or substituted ureas with amino acid esters (Scheme 2) while compounds **16–17** were prepared by deprotection of BOC-amino-acylureas (Scheme 3). These diacylamines are stable compounds, in contrast to the diacylamines of amino acids and carboxylic acids or aminoacyl-dicyclohexylureas which rearrange to acylamino acid amides in the presence of bases even at room temperature.^{1,13}



Acyl = Phe, Phg, Ac-Phg, BOC-Gly, BOC-Pro, BOC-β-Ala, BOC-Phg; R = H, cyclohexyl, phenethyl

Scheme 2



Aminoacyl = Gly, Pro; R = phenethyl

Scheme 3

The phenylalanylureas (**12** and **13**), prepared by the reaction of D- and L-Phe-OEt, were optically active but acylations with BOC amino acid esters gave optically inactive products (**5** and **9**).

The process shown in Schemes 1 and 2 appear to be general for the preparation of diacylamines from esters with amides (with the two noted exceptions) and is not limited to the reaction of the esters with formamide,¹⁴ nor to the preparation of open chain acylureas.¹⁵ It is suggested that this straightforward synthesis of diacylamines of amino acids and carbamic acids (amino-acylureas) makes it possible to screen for antineoplastic or anticonvulsant activity, and also to prepare pseudo-peptides of carbamic acids, a class of compounds not yet investigated.

Experimental

The following compounds were prepared: (a) **Diacylamines of two carboxylic acids**: N-Benzoyl-trimethylacetamide, **1**, N-Phenylacetyl-trimethylacetamide, **2**, N-Isobutyryl-benzamide,⁸ **3**, N-(Acetyl-DL-phenylglycyl)-benzamide, **4**, N-(BOC-DL-alanyl)-trimethylacetamide, **5**; (b) **Diacylamines of N-acyl-amino acids and carbamic acids**: N-(BOC-DL-phenylglycyl)-urea, **6**, N-(Ac-DL-phenyl-glycyl)-urea, **7**, N-(BOC-glycyl)-N'-cyclohexylurea, **8**, N-(BOC-DL-prolyl)-N'-phenethylurea, **9**, N-(BOC-glycyl)-N'-phenethylurea, **10**, BOC-β-alanylurea., **11**; (c) **Diacylamines of amino acids and carbamic acids**: N-(L-phenylalanyl)urea,

12, N-(D-phenylalanyl)urea, **13**, N-(DL-phenylglycyl)urea, **14**, N-(3-aminobenzoyl)urea,⁶ **15**; N-DL-Pro-N'-phenethylurea.HCl, **16**, N-Glycyl-N'-phenethylurea.HCl, **17**.

Preparation of 1–5. Carboxylic esters and carboxylic amides were reacted with Na-methoxide (25% in MeOH) in N,N-dimethylacetamide (DMAA) at 25 °C for 30 min. The molar ratio of carboxylic esters and methoxide was 1:5 in each case. Alcohols (excess solvent and reaction product, Scheme 1) were evaporated in vacuum. Diacylamines were isolated from the ethyl acetate extraction of the acidified (dil. HCl) mixtures (**1**, **2**, **3**, **5**) or by filtration (**4**). The reaction mixture of the BOC derivative, **5**, was neutralized with citric acid solution before extraction. Yields for **1–5** were in the 40–80 % range. Additional details: **1**. Methyl benzoate, 0.015 mol, trimethylacetamide, 0.03 mol. Mp 107–109 °C (hexane). Mw 205.25. **2**. Same as **1**, using methyl phenylacetate, 0.015 mol, trimethylacetamide, 0.03 mol. Mp 97–100 °C (hexane). Mw 219.27. **3**. Same as **1**, using methyl benzoate, 0.015 mol, isobutyramide, 0.03 mol. Mp 150 °C (EtAc-hexane) (ref 8: 149–150 °C). Mw 191.22. **4**. Ac-DL-Phg-OMe, 0.015 mol, benzamide 0.02 mol, Mp 115–118 °C (EtAc). Mw 296.31. **5**. BOC-L-Ala-OMe, 0.015 mol, trimethylacetamide, 0.03 mol. Mp 103–106 °C (hexane). Mw 272.34; $[\alpha]_D 0$ (c 2, DMAA).

Preparation of 6–11. N-protected amino acid esters, 0.01 mol, urea, 0.1 mol or N-alkyl ureas, 0.01 mol and NaOMe 0.05 mol (25% solution in MeOH) were reacted as above. The reaction mixtures were acidified with citric acid and the products were isolated by EtAc extraction (**8–10**) or by filtration (**6**, **7**, **11**). Yields were 50–80%. Additional details: **6**. BOC-DL-Phg-OMe and urea reacted. The crude product was washed with cold MeOH-ether. Mp 203–206 °C. Mw 293.32. **7**. Ac-DL-Phg-OMe and urea reacted. Mp 203–205 °C (water). Mw 235.24. **8**. BOC-Gly-OMe and cyclohexylurea reacted. Mp 143–145 °C (ether). Mw 299.36. **9**. BOC-L-Pro-OMe and phenethylurea reacted. Mp 154–157 °C (EtAc-hexane). $[\alpha]_D 0$ (c 2, DMAA). Mw 361.43. **10**. BOC-Gly-OMe and phenethylurea reacted. Mp 118–119 °C (ether). Mw 321.27. **11**. BOC- β -Ala-OEt and urea were reacted. Mp 148–151 °C (EtAc). Mw 231.25.

Preparation of 12–15. Amino acid ester hydrochloride (0.01 mol) and 0.1 mol urea were reacted with 0.05 mol NaOMe in 5 ml DMAA for 30 min at 25 °C as above. The reaction mixtures were slightly acidified with HCl, made alkaline with ammonium hydroxide, the products isolated by EtAc extraction and HCl salts prepared with EtOH.HCl. Yields: 70–86%. Additional details: **12**. Mp 146–149 °C (MeOH); $[\alpha]_D -14.51$ (c 3, DMAA). Mw 207.23. Mp (HCl salt): 192–194 °C (EtOH-ether). **13** (L isomer). Mp 146–148 °C (MeOH); $[\alpha]_D +13.5^\circ$ (c 3, DMAA). Mw 207.23. **14**. Mp (HCl salt): 210–212 °C (MeOH-ether). Mw 229.66. Crystalline **15** was obtained upon the acidification of the reaction mixture of ethyl 3-aminobenzoate and urea. Mp >300 °C (MeOH-water). Mw 179.18.

Preparation of 16 and 17. 500 mg portions of BOC-amino-acylureas **9** and **10** and were reacted with 10 mL TFA for 1 h at 25 °C. The evaporated mixtures were treated with NH₄OH, the separated bases filtered, and HCl salts made in EtOH.HCl. Additional details: **16**. Yield of crude salt: 86%. Mp 218–220 °C (EtOH). Mw 297.77. **17**. Yield of crude salt: 68%. Mp 180–183 °C. Mw 257.71.

Characterization. The molecular weight of each product was confirmed by electrospray mass spectrometry. NMR data (ppm) for representative compounds: **4**. 11.25 (s, 1H, NH imide); 8.65 (s, 1H, NH amide); 7.79–7.33 (m, 10H, CH-phenyl); 6.05 (m, 1H, CH-N), 1.91 (s, 3H, CH₃). **12**. 10.67 (s, 1H, NH imide); 8.56 (s, 3H, NH₃⁺); 7.42 (d, 2H, NH₂); 7.35–7.25 (m, 5H, CH-phenyl); 4.17 (s, 1H, CH-N); 3.11 (m, 2H, CH₂). **14**. 10.80 (s, 1H, NH imide); 8.86 (s, 3H, NH₃⁺); 7.55 (d, 2H, NH₂); 7.46 (m, 5H, Ch-phenyl); 5.07 (s, 1H, CH-). **17**. 10.7 (S1H, NH imide); 8.33 (S3H, NH₃⁺); 7.97 (S1H, NH amide); 7.37–7.18 (m, 5H, phenyl); 3.75 (S2H, CH₂ glycine); 3.42 (m, 2H α CH₂); 2.77 (t, 2H, β CH₂Ph).

Acknowledgement: Supported by T.J. Martell Foundation for Leukemia, Cancer and AIDS Research.

References

1. Wendlberger, G. In *Methoden der Organischen Chemie*; Wunsch, E., Ed.; Thieme: Stuttgart, 1974; Vol. XV/2, Part 2, pp 335–355.
2. Schumacher, H.; Blake, D. A.; Gillette, J. R. *Fed.Proc.* **1967**, 2642, 730.
3. Huang, P. H.; McBride, W. G. *Teratog Carcinog. Mutagen.* **1997**, 17, 5.
4. Jenkins, V. K.; Mayer, R. T.; Perry, R. R. *Invest. New Drugs* **1980**, 2, 19.
5. Filov, V. A. *Vopr.Onkol.* **1997**, 43, 120.
6. Jiang, J. D.; Wang, Y.; Roboz, J.; Holland, J. F.; Bekesi, J. G. *Cancer Res.* **1998**, 58, 2126.
7. Schafer, H. In *Handbook of Experimental Pharmacology*; Frey, H. H.; Janz, D. Eds.; Springer: Berlin, 1985; Vol. 74, pp 199–236.
8. Bates, R. B.; Fletcher, F. A.; Janda, K. D.; Miller, W. A. *J. Org. Chem.* **1984**, 49, 3038.
9. Wheeler, O. H. In *The Chemistry of Amides*; Zabicky, J., Ed.; Interscience: New York, 1970; pp 335–375.
10. Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; pp 381–411.
11. Dox, A. W.; Yoder, L. *J. Amer. Chem. Soc.* **1922**, 44, 1141.
12. Allred, E. L.; Hurwitz, M. D. *J. Org. Chem.* **1965**, 30, 2376.
13. Schon, I.; Friss, J.; Kisfaludi, L. *Acta Chim. Hung.* **1978**, 98, 215.
14. Jagdmann, G. E.; Munson, H. R.; Gero, T. W. *Synth. Commun.* **1990**, 20, 1203.
15. Weisz, I.; Ruff, E.; Otvos, L. (Hungarian Patent HU 33775); *Chem Abstracts*, **1985**, 103, 53708.