

SYNTHESIS OF AZAPEPTIDES FROM HINDERED AMINES
LEADING TO NOVEL GROWTH HORMONE SECRETAGOGUES

Thomas Kruse Hansen*

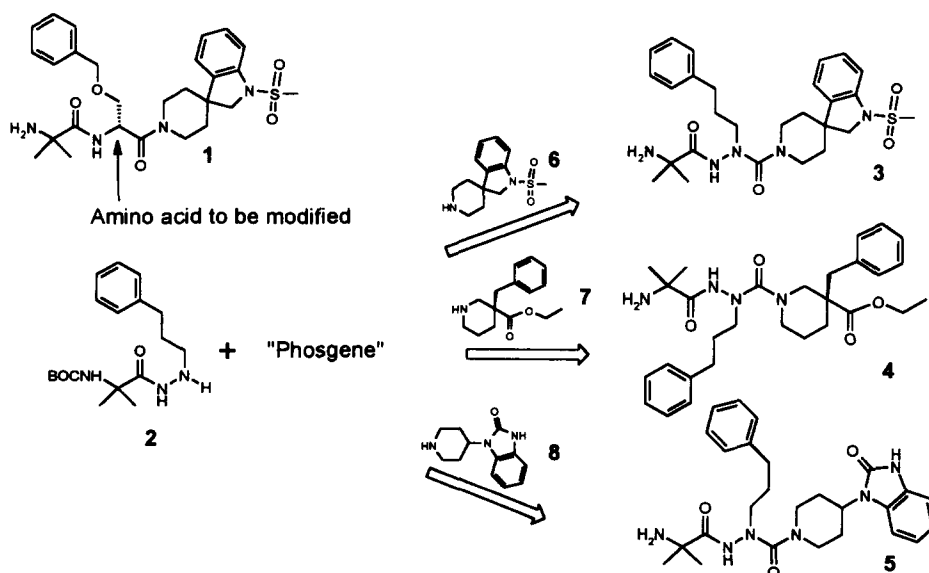
Medicinal Chemistry Research IV, Novo Nordisk A/S, Novo Nordisk Park, 2760 Måløv, Denmark

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Abstract: Preparations of aza analogues of known potent growth hormone secretagogues (GHS) were unsuccessful using known methods for preparation of azapeptides when hindered amines were employed. We now report a coupling method using bis(pentafluorophenyl)carbonate as a “balanced reactivity” phosgene equivalent to solve these problems.

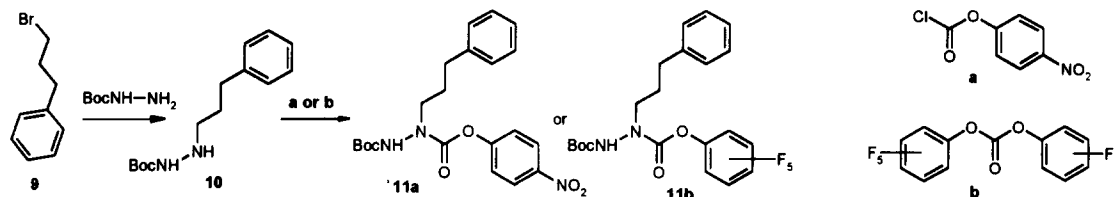
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During our ongoing program directed at finding new and improved growth hormone secretagogues¹ we became interested in preparing azapeptide² analogs of known GHSs such as MK677 (1) as the interest in such compounds continues to expand. There is a plethora of possible indications for such compounds including treatment of burns, for Turners syndrome, for sleep enhancement, to reverse catabolic conditions and in reducing some of the effects of age.¹ All known GH-secretagogues contain one or more chiral, nonbiogenic D-amino acids that makes the synthesis of such compounds more expensive and lengthy. Azapeptides in contrast, are achiral and reported to be easy to synthesize² and to offer a good chance of retaining the biological activity of the parent peptide.



* E-mail: TKHa@novo.dk Fax: (+45)44663450

Based on precedent in the literature² it appeared to be a relatively simple task to prepare compounds such as **3** and **4** (close or direct aza-analogs of known GHSs) and **5** (novel type) from a substituted hydrazine such as **2**, an amine such as **6,7** or **8** and phosgene or a phosgene equivalent. However, we quickly learned that activation at the dipeptide level was troublesome and resorted to Boc-hydrazine as the starting material. Direct alkylation with 3-bromopropylbenzene (**9**) to give **10** worked well (85% using a 2 fold excess of Boc-hydrazine) and was, in our hands, superior to reductive alkylation.³ Reaction with 4-nitrophenyl chloroformate produced crystalline **11a** in 95% yield.



This material reacted with primary amines but not with secondary amines or piperidines (like **6-8**) and there were in fact hardly any references to such transformations in the literature.⁴ As we took this to be a reactivity problem we investigated phosgene, triphosgene and carbonyldiimidazole as *in situ* coupling agents with a number of variations in temperature, solvent and order of addition but with no success.³ Apparently, these reactants are too reactive and cause polymerizations.² Looking for “intermediate reactivity” agents we tried bis(pentafluorophenyl)carbonate³ and obtained stable crystalline **11b** with no signs of urea formation. Using this reagent in DMF (DCM did not work) we were able to carry out the desired couplings in moderate to good yields (50-60%). The subsequent steps (deprotection with TFA, EDAC/HOAt mediated coupling of BocAib followed by a final deprotection with TFA) were trivial and produced the desired compounds **3**, **4** and **5** in good yields. We believe that this method can be extended to many other hindered amines and expand the scope of azapeptides significantly. The biological potencies of **3**, **4** and **5** were measured in a rat pituitary cell assay and we observed EC₅₀ of 14nM, 1175nM and 15nM indicating that **3** is about ten times less potent than **1** but **3** is still a very potent compound whereas **4** has lost a potency factor of 1000. For compound **5** no reference compound has been made.

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Notes and References

1 For leading references to this area consult: (a) Bowers, C. Y.; Momany, F. A.; Reynolds, G. A.; Hong, A. *Endocrinology* **1984**, *114*, 1531. (b) Schoen, W. R.; Pisano, J. M.; Prendergast, K.; Wyvratt, M. J.; Fisher, M. H.; Cheng, K.; Chan, W. W. S.; Butler B.; Smith, R. G.; Ball, R. G. *J. Med. Chem.* **1994**, *37*, 897-906. (c) F. A. Momany, C. Y. Bowers, “Growth Hormone Secretagogues”, Eds. B. B. Bercu and R. F. Walker, Springer-Verlag, New York, **1996**. (d) DeVita, R. J.; Wyvatt, M. J. *Drugs of the Future*, **1996**, *21*, 273. (e) Strobl, J. S.; Thomas, M. J. Human growth hormone. *Pharmacological Reviews* **1994**, *46*, 1-34. (f) Mayo, K.E. *Molecular Endocrinology* **1992**, *6(10)*:1734-1744, (g) Hansen, T.K.; Ankersen, M.; Hansen, B.; Raun, K.; Nielsen, K. K.; Lau, J. Pechke B.; Lundt, B.; Thøgersen H.; Johansen, N. L.; Madsen, K.; Andersen, P. H. *J. Med. Chem.* **1998**, *41*, 3705-14

2 Gante, J., *Synthesis*, **1989**, 405-413

3 Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539-44

4 For proline as an exception see Andre, F.; Marraud, M.; Boussard, G. *Tetrahedron. Lett.* **1996**, *37*, 183-186.