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A new synthesis of 1,2,4-triazolin-5-ones: application to the convergent synthesis of an NK_1 antagonist

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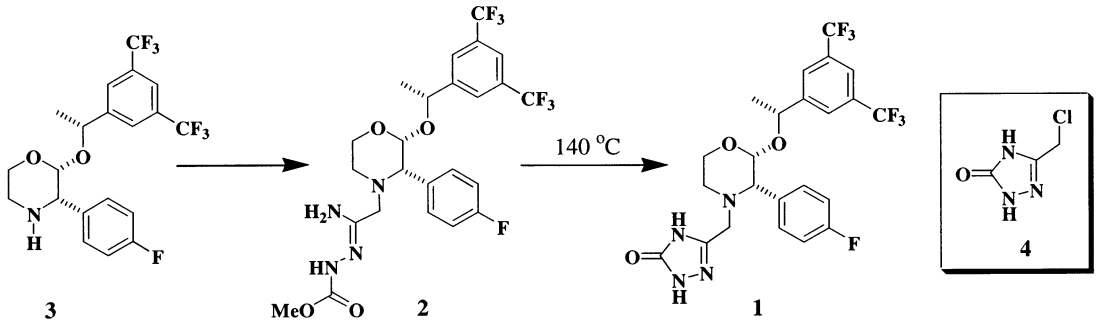
Abstract

Chlorotriazolinone **4** has been synthesised in a single step via the novel condensation of semicarbazide hydrochloride with orthoester **8**. Alkylation of secondary amine **3** with compound **4** proceeds in 99% yield to afford the target NK_1 antagonist **1**. © 2000 Published by Elsevier Science Ltd.

Substance P is an undecapeptide belonging to the tachykinin family of neurotransmitters which acts preferentially at NK_1 receptors.[1] Compound **1** is a potent, long-lasting, non-peptidic, substance P antagonist. It is, therefore, a potential therapeutic candidate for a range of afflictions including migraine and chemotherapy-induced emesis.[2] The pendant 1,2,4-triazolin-5-one heterocycle of **1** was previously introduced via a two-step protocol that included a high temperature cyclisation of intermediate **2** (Scheme 1).[2] For development purposes, we hoped to



Scheme 1.

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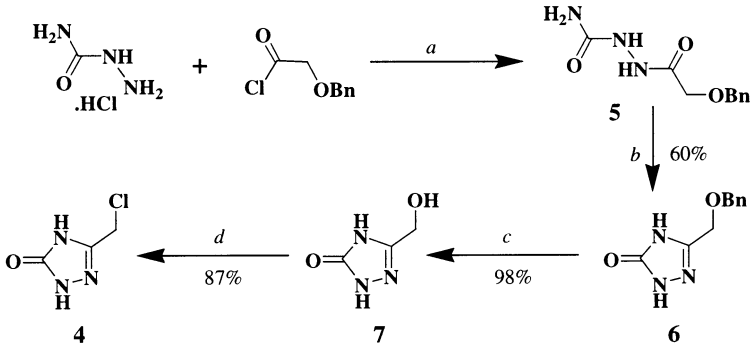
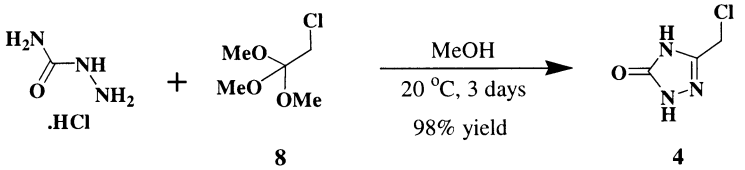
simplify this end-game strategy using the alkylation of secondary amine **3**[2] with the previously unreported chlorotriazolinone **4**. We now report the results of this alkylation reaction and the first reported synthesis of compound **4** via a novel one-step condensation of two commercially available starting materials. The ready access to **4** should now simplify its introduction to a range of other pharmaceutical and agrochemical compounds.

Our initial synthesis of **4** used the base-catalysed cyclisation of an acyl semicarbazide (Scheme 2). Hence, benzyloxyacetyl chloride was condensed with semicarbazide hydrochloride under modified Schotten–Baumann conditions to give crude adduct **5**.[3] This was not purified but, instead, was heated in dilute NaOH to induce cyclisation, thus giving triazolinone **6** in 60% yield from benzyloxyacetyl chloride. Hydrogenolytic removal of the benzyl protecting group gave the water soluble alcohol **7**[4] (98% yield) and treatment of this compound with thionyl chloride afforded triazolinone **4** as a stable crystalline solid in 87% yield.



Scheme 2. (a) NaOH, THF/H_2O (5:1), 0°C, 2 h; (b) NaOH (2 M aq.), reflux, 5 h; (c) Pd on C, HCO_2NH_4, MeOH/H_2O (10:1), 60°C, 4 h; (d) $SOCl_2$, CH_3CN, 20°C, 18 h

While this synthesis of compound **4** allowed the subsequent alkylation reaction to be studied (vide infra), the cost of the starting acid chloride and the number of steps involved detracted from its viability for large scale synthesis. After examining several unsuccessful routes starting from chloroacetyl chloride, a one-step synthesis of compound **4** was realised, as shown in Scheme 3. By simply reacting semicarbazide hydrochloride with the commercially available orthoester **8**,[5] chlorotriazolinone **4** was isolated cleanly in 98% yield.[6] While the condensation of orthoesters with nitrogenous molecules leading to heterocycles is common,[7] to the best of our knowledge, *this is the first condensation of an orthoester with semicarbazide hydrochloride to afford a triazolinone derivative* and represents one of the simplest syntheses of these biologically useful heterocycles.[8]

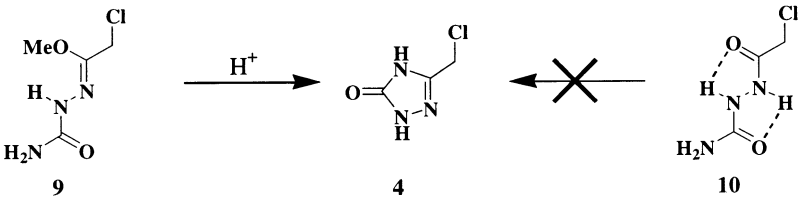


Scheme 3.

While optimising this reaction, we found that excess orthoester (2.20 equiv.) was necessary for consumption of the semicarbazide. This was due to competitive acid-catalysed decomposition of the orthoester leading to the production of methyl chloroacetate and chloromethane. Buffering

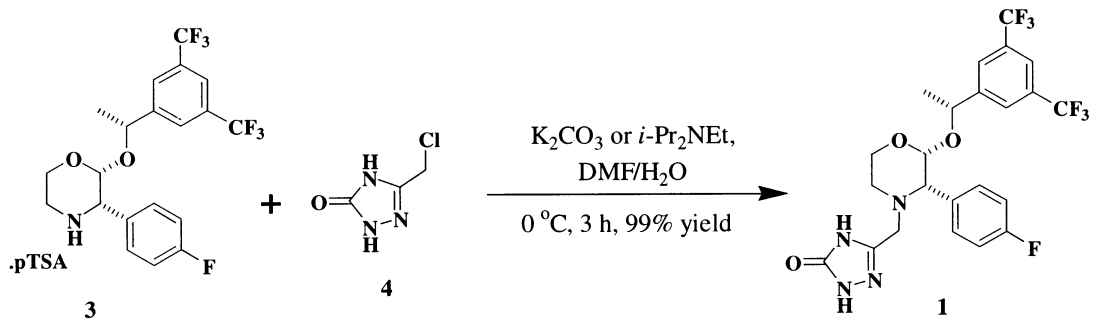
the reaction with base resulted in no product formation, although decomposition of **8** was prevented. We hoped chloride attack on a methyl group of the orthoester might be prevented by the use of an alternate trialkyl orthoester (e.g. triethyl instead of trimethyl), however, a lower yield of product resulted. When conducting the reaction in refluxing methanol, the yield decreased further (<20%) indicating the sensitivity of the orthoester.

It is assumed that the reaction proceeds in a step-wise fashion via intermediate **9** (Scheme 4). This compound was not observed in the crude mixtures, probably indicating a facile cyclisation to product. In contrast, we were unable to cyclise acyl semicarbazide **10** even at elevated temperatures with added acid catalysts. A possible explanation for this dichotomy is that an intramolecular H-bonding arrangement in compound **10** hinders cyclisation.



Scheme 4.

The alkylation of secondary amine **3** with chloride **4** was carried out at 0°C using a variety of bases (Scheme 5). Optimum conditions[9] used K_2CO_3 or *i*-Pr_2NEt with a slight excess of triazolinone **4** (1.03 equiv.) and the final product was isolated in 99% yield. Surprisingly, the use of wet DMF (1% water) led to an acceleration of the alkylation, even for the homogeneous reaction using *i*-Pr_2NEt as base.



Scheme 5.

In conclusion, the first synthesis of chlorotriazolinone **4** is reported. This is best achieved by the novel condensation of semicarbazide hydrochloride with orthoester **8**. It is anticipated that by varying the orthoester component of this reaction, the synthesis of a range of triazolinones will be possible.[10] Compound **4** should be invaluable for incorporating the triazolinone nucleus into a range of biologically active molecules in a single alkylation step. This has been demonstrated here by the development of a streamlined process for the synthesis of the potent substance P antagonist **1**.

Acknowledgements

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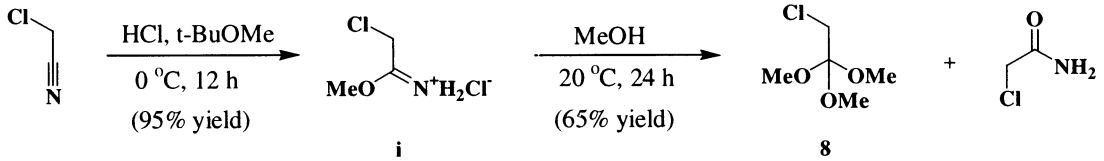
2. Hale, J. J.; Mills, S. G.; MacCoss, M.; Finke, P. E.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Chicchi, G. G.; Kurtz, M.; Metzger, J.; Eiermann, G.; Tsou, N. N.; Tattersall, F. D.; Rupniak, N. M. J.; Williams, A. R.; Rycroft, W.; Hargreaves, R.; MacIntyre, D. E. *J. Med. Chem.* **1998**, *41*, 4607.
3. Apart from compound **5** which was used crude in the subsequent step, all new compounds gave spectroscopic data in agreement with the assigned structures.
4. Shvaika, O. P.; Baranov, S. N.; Artemov, V. N. *Dokl. Akad. Nauk SSSR* **1969**, *186*, 1102; *Chem. Abstr.* **1969**, *71*, 70540r.
5. 2-Chloro-1,1,1-trimethoxyethane (**8**) is available from Aldrich Chemical Company (cat. number 43 794-8). Two literature syntheses of this compound have been reported: Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064; McElvain, S. M.; Nelson, J. W. *J. Am. Chem. Soc.* **1942**, *64*, 1825. The most recent involved the radical chlorination of trimethyl orthoacetate, while the earlier used the methanolysis of imidate salt **i**, itself formed by Pinner reaction of chloroacetonitrile. We examined the latter route and found that chloroacetamide was the primary by-product from the methanolysis reaction, however, it was not observed in the crude material as it partitioned to the aqueous phase. This side reaction is related to the acid-catalysed decomposition of orthoester **8** in the triazolinone synthesis where chloromethane is also co-produced.



Interestingly, condensation of semicarbazide·HCl with imidate **i** only led to triazolinone **4** when the reaction was conducted in methanol. Orthoester **8** is assumed to be an intermediate in this condensation and it was observed when following the reaction by ^{1}H NMR spectroscopy.
6. A mixture of semicarbazide·HCl (100 g, 0.90 mol), orthoester **8** (305 g, 2.0 mol) and MeOH (1.0 L) was stirred at 20°C for 3 days. The solvent was then removed under reduced pressure and toluene (1.0 L) was added and the slurry concentrated further to remove residual MeOH. The mixture was then cooled to 0°C and filtered to afford 3-chloromethyl-1,2,4,-triazolin-5-one (**4**) (117 g, 98%) as a white solid (mp 197–199°C), ^{1}H NMR (250 MHz, DMSO-d_6) 4.43 (2H, s, C$\underline{H}_2$), 11.48 (1H, s, N$\underline{H}$) and 11.64 (1H, s, N$\underline{H}$); ^{13}C NMR (62.9 MHz, DMSO-d_6) 36.9 (Cl$\underline{C}$H$_2$), 144.6 (CH$_2\underline{C}$=N) and 156.9 (NH$\underline{C}$ONH); Anal. calcd for $C_3H_4ClN_3O$: C, 26.98; H, 3.02; Cl, 26.55; N, 31.47. Found: C, 27.01; H, 2.92; Cl, 26.34; N, 31.21.
7. For example, the use of **8** in the synthesis of benzothiazoles/benzoxazoles and oxazoles: Mylari, B. L.; Scott, P. J.; Zembrowski, W. J. *Synth. Commun.* **1989**, *19*, 2921; Kamata, K.; Sato, H.; Takagi, E.; Agata, I.; Meyers, A. I. *Heterocycles* **1999**, *51*, 373.
8. For other syntheses of 3-substituted-1,2,4-triazolin-5-ones, see: (a) Rigo, B.; Valligny, D.; Taisne, S. *Synth. Commun.* **1988**, *18*, 167; (b) Milcent, R.; Nguyen, T.-H. *J. Heterocycl. Chem.* **1986**, *23*, 881; (c) Adembri, G.; Camparini, A.; Ponticelli, F.; Tedeschi, P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1703; (d) Scott, F. L.; Lambe, T. M.; Butler, R. N. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1918; (e) Ün, R.; Ikizler, A. *Chim. Acta Turc.* **1975**, *3*, 113.
9. A mixture of chlorotriazolinone **4** (8.30 g, 62.2 mmol) in DMF (80 mL) was added dropwise to a cooled (0°C), stirred mixture of amine·*p*-TSA **3** (36.8 g, 60.4 mmol) and powdered K_2CO_3 (9.18 g, 66.4 mmol) in DMF/water (122 mL, 60:1). After 2 hours, water (400 mL) was added and isolation of the resulting precipitate afforded compound **1** (31.8 g, 99%), which was identical (^{1}H NMR, ^{13}C NMR, mp, HPLC retention time) to that previously reported.[2]
10. The condensation of semicarbazide·HCl with trimethyl orthoformate (rt, MeOH, 1 h) afforded the parent triazolinone in quantitative yield.