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Solid Phase Synthesis of Cyanoacetamidines: Fast Access to Potential Bioisosteres of Acceptor-Substituted Guanidines

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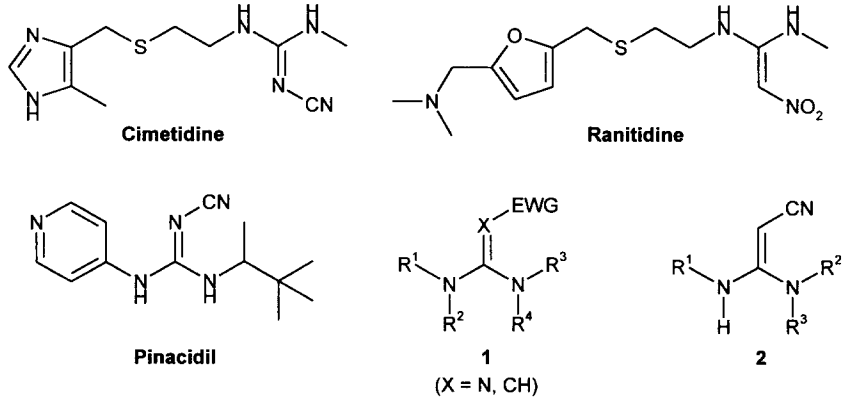
Abstract: A synthesis of cyanoacetamidines has been developed, which can be realized on solid support. Reaction of resin-bound cyanoacetic acid with aromatic isothiocyanates yielded thioamides, which could be condensed with primary or secondary aliphatic or aromatic amines in the presence of EDC to yield ketene aminals. TFA-mediated cleavage from the support with concomitant decarboxylation gave cyanoacetamidine trifluoroacetates in purities up to 83% (HPLC, 254 nm). © 1997 Elsevier Science Ltd.

Acceptor-substituted guanidines and their bioisosteres **1** are important substructures of modern drugs.[1] As illustrative examples the histamine H_2 receptor antagonists Cimetidine[2] and Ranitidine,[3] used for the treatment of gastric ulcer, and the antihypertensive potassium channel opener Pinacidil[4] are sketched below (Scheme 1).

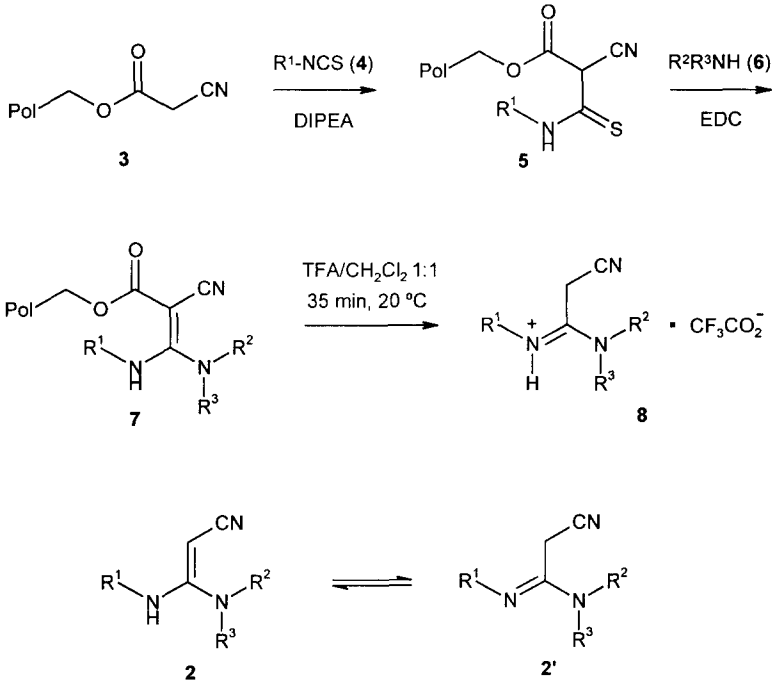


Scheme 1. Examples for drugs containing acceptor-substituted guanidines or bioisosteres thereof. R^1-R^3: see Scheme 3

In view of the broad applicability of compounds as **1**, we reasoned that a solid phase synthesis of bioisosteres of such compounds could become a very valuable tool for lead discovery. Parallel solid phase synthesis[5] should permit the fast and automated production of arrays of single compounds or mixtures of **1**, useful for high throughput screening.

The present work aimed at the development of a solid phase synthesis of cyanoacetamidines **2**, which have not yet been used extensively as bioisosteres of acceptor-substituted guanidines.[6] Several different

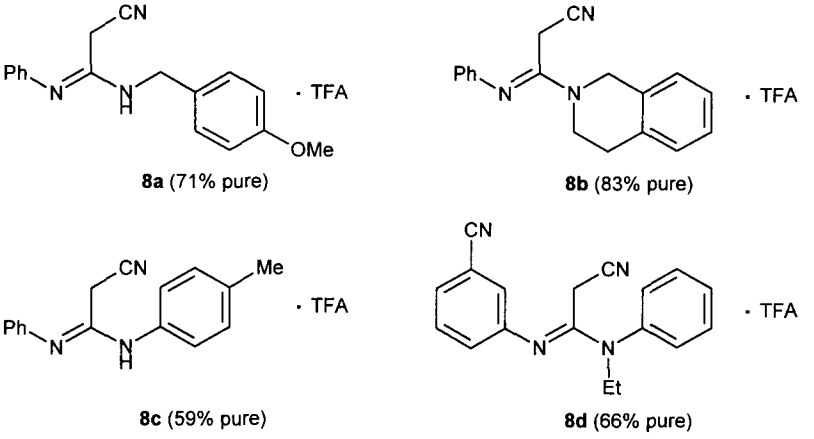
methods for the preparation of amidines **2** have been reported,[7] but none of these seemed suitable for realization on a polymeric support. However, after some experimentation we found a new procedure, which could be carried out on a polystyrene resin[8] and which yielded crude products of high purity (Scheme 2).



Scheme 2. Solid phase synthesis of cyanoacetamidine trifluoroacetates **8**; Pol: polystyrene with Wang linker; R^1-R^3: see Scheme 3; DIPEA: diisopropylethylamine; EDC: *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride; TFA: trifluoroacetic acid

Cyanoacetic acid was esterified with Wang resin and the resulting ester **3** was *C*-thioacylated with isothiocyanates **4** in the presence of Hünig-base.[9] In the key-step of this synthesis the resulting thioamides **5** were condensed with primary or secondary aliphatic or aromatic amines **6** in the presence of *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimid hydrochloride (EDC), to yield ketene aminals **7**.[10] This conversion is closely related to a published procedure for the transformation of cyanothioureas into cyanoguanidines by treatment of the former with amines and EDC (in solution).[11] Similarly as reported,[11] EDC was essential in our procedure and could neither be omitted nor replaced by other carbodiimides.

Acidolytic cleavage of the ketene aminals **7** from the support, followed by spontaneous decarboxylation, yielded the desired amidine trifluoracetates **8**, which may be deprotonated to give mixtures of stereoisomeric and tautomeric forms of the amidines **2**.[7] Examples of compounds **8** prepared by this method are shown in Scheme 3.[12]



Scheme 3. Examples for amidine trifluoroacetates **8** prepared on solid support. The given purities (of crude products) were determined by HPLC at 254 nm.[11]

The purity of the crude products **8**[12] was high when *aromatic* isothiocyanates **4** and *primary, aliphatic* amines **6** were used in this reaction sequence. The combination of aromatic isothiocyanates **4** with primary or secondary aromatic amines **6** tended to yield less pure products. Very inpure products or no products **8** at all were obtained when *aliphatic* isothiocyanates **4** were used as reagents. Cleavage time resulted to be extremely critical, and had to be limited to maximally 1 h, since products **8** slowly decomposed under the acidic conditions required for cleavage.

In conclusion a protocol for the solid phase synthesis of cyanoacetamidines with variable substituents is disclosed herein. This reaction sequence is based on easily available starting materials and can be realized at ambient temperature. It is therefore suitable for standard peptide synthesizers, thus permitting the fast preparation of numerous new compounds for high throughput screening.

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8. *Typical procedure: N-(4-methoxybenzyl)-N'-(phenyl)cyanoacetamidine trifluoroacetate (**8a**):* To a suspension of Wang resin (20.0 g, 19.2 mmol, Novabiochem, loading: 0.96 mmol/g) in dichloromethane (DCM, 100 mL) cyanoacetic acid (30.0 g, 353 mmol) and DMF (100 mL) were added. While stirring and cooling diisopropylcarbodiimide (25 mL, 161 mmol) was portionwise added. When the addition was completed, 4-dimethylaminopyridine (10 mL of a 1 M solution in DMF) was added and the resulting mixture was stirred at room temperature for 15 h. The mixture was filtered and the resin was washed with DMF, DCM and methanol. After drying, approx. 20 g of resin **3** was obtained. To this resin (0.30 g, approx. 0.3 mmol, swollen in DCM) DMF (4.0 mL), diisopropylethylamine (0.8 mL) and phenylisothiocyanate (0.54 mL, 4.5 mmol) were added. The resulting mixture was shaken for 16 h, filtered, washed with DMF (3 x 6.0 mL) and a freshly prepared mixture of EDC (0.95 g, 4.95 mmol), DMF (5.0 mL) and 4-methoxybenzylamine (0.40 mL, 3.03 mmol) was added. The mixture was shaken for 24 h, filtered, and the resin was thoroughly washed with DMF, methanol, DCM and 10% acetic acid in DCM. It was suspended in DCM (3.0 mL) and TFA (3.0 mL) and shaken for 35 min. Carbon tetrachloride (5.0 mL) was added and after filtration and rinsing with DCM the filtrates were concentrated. 84 mg (71%) of **8a** were obtained as an oil (71% pure by HPLC, 254 nm), which crystallized at room temperature within 48 h. Recrystallization (ethyl acetate/methanol/heptane) yielded 22 mg (19%) of the title compound as colourless crystals, mp 161-163 °C. LCMS: elution at 7.2 min; MH^+ calcd.: 280, found: 280. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, br, 3 H), 3.89 (s, br, 2 H, exchangeable with D_2O), 4.60 (s, br, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.30-7.55 (m, 5 H), 10.25 (s, br, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.26 (t), 46.17 (t), 55.10 (q), 113.98 (d), 125.66 (d), 126.71 (d), 127.62 (d), 129.19 (d), 137.50 (s, br), 154.36 (s, br), 159.29 (s). Anal. Calcd. for $C_{19}H_{18}F_3N_3O_3$ (393.36): C, 58.01; H, 4.61; N, 10.68. Found: C, 57.98; H, 4.68; N, 10.47.
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10. This EDC-mediated condensation reaction also proceeds in solution (12-47% yield, Zaragoza, F.; unpublished results). Higher yields of ketene aminals were however obtained with mercury(II) oxide as desulfurizing agent. Peseke, K. Ger. (East) Patent 98914, **1973** [*Chem. Abstr.* **1974**, *80*, 59723t].
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12. All products were analyzed by LCMS, ^{1}H NMR, ^{13}C NMR and HPLC (254 nm and 214 nm). The molecular formulas were confirmed either by elemental analysis or by high-resolution MS. We acknowledge Dr. D. Böhler and Dr. G. Remberg (University of Göttingen, Germany) for the recording of HRMS spectra.

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