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Solid-Phase Synthesis of Substituted 1,2,3-Triazoles

Florencio Zaragoza* and Susanne Vejle Petersen

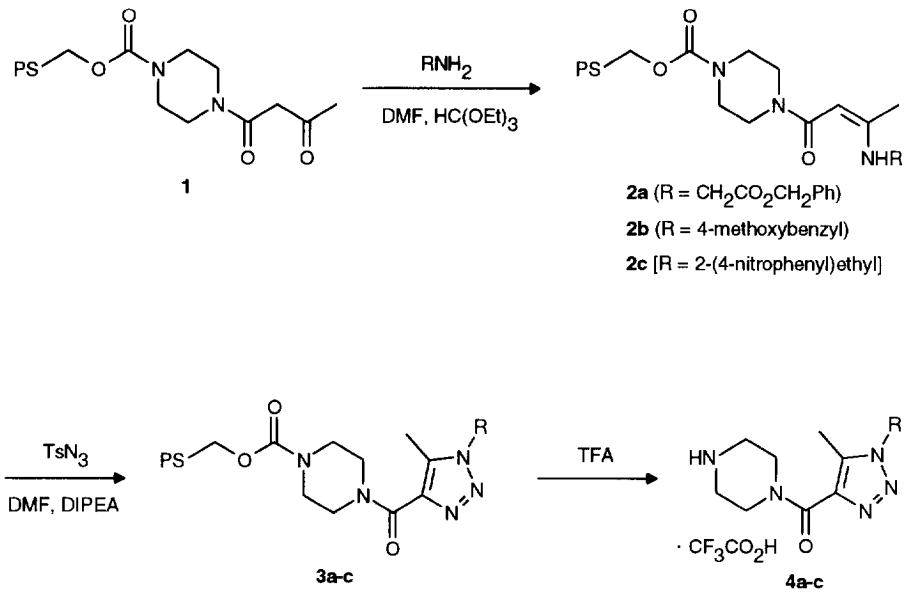
Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark
Telefax: (+45) 4466 3450, e-mail: flo@novo.dk

Abstract: Diversely substituted 1,2,3-triazoles have been synthesized on a solid support. A resin-bound 3-oxobutyramide could be effectively condensed with primary aliphatic amines. The resulting 3-amino-2-butenoic acid amides were then cyclized by treatment with tosyl azide in the presence of a tertiary amine. Acidolytic cleavage from the support yielded the corresponding 1,2,3-triazoles in purities up to 82% (HPLC). Copyright © 1996 Elsevier Science Ltd

Combinatorial chemistry is becoming increasingly important in pharmaceutical research as an efficient tool for the rapid identification and optimization of new leads.[1] Solid-phase synthesis is playing a decisive role in the ongoing development of combinatorial chemistry, mainly because it offers high synthetic flexibility as well as the possibility of automatization. However, the number of different reactions applicable to solid-phase synthesis, although rapidly growing, is still small, if compared to the vast repertoire of synthetic methodology available for synthesis "in solution". In particular, the access to heterocyclic compounds by solid-phase synthesis[2] is urgently required, since small, substituted heterocycles offer a high degree of structural diversity and have proven to be exceptionally useful in many applications.[6]

In this communication a new synthetic sequence is presented, which allows the solid-phase synthesis of substituted 1,2,3-triazoles (see scheme). While investigating the chemistry of the support-bound (3-oxobutyryl)piperazine **1**[3] we found, that a condensation with primary, aliphatic amines readily occurred in the presence of triethyl orthoformate.[4] The resulting 3-amino-2-butenoic acid amides **2a-c** could successively be cyclized to give the 1,2,3-triazoles **3a-c** by treatment with tosyl azide and a tertiary amine.[5] Treatment of these resin-bound 1,2,3-triazoles **3a-c** with trifluoroacetic acid in dichloromethane, followed by removal of the solvents, yielded the crude triazoles **4a-c** as trifluoroacetates in purities up to 82% (^{1}H NMR, HPLC).

The mild reaction conditions used in this synthetic sequence enabled its application to building blocks with a large number of different functionalities. Only when electron-rich benzylic amines, such as benzhydrylamine, were used in the enamine-forming step, mixtures of products were obtained. This may be due to the high stability of the corresponding benzylic carbocations, which could give rise to solvolysis of the initially formed triazoles during the acidolytic cleavage.



Abbreviations: PS: polymeric support (polystyrene with Wang linker); TsN_3: *p*-toluenesulfonyl azide; DIPEA: diisopropylethylamine; TFA: trifluoroacetic acid.

In conclusion, a solid-phase protocol for the synthesis of 1,2,3-triazoles with in principle three independently variable substituents is disclosed herein. Although only the conversion of the resin-bound (3-oxobutyryl)piperazine **1** into different triazoles has been described here, this sequence may also be applicable to other resin-bound amines (e.g. α-amino acids, other diamines or resins with a Rink linker) and to other 3-oxoalkanoic acids, thus permitting the fast and easy preparation of numerous, highly diverse non-oligomeric compounds as potential drug candidates.[6]

EXPERIMENTAL

General procedures. Wang resin (p-benzyloxybenzylalcohol resin) with a substitution of 0.94 mmol/g was purchased from Calbiochem-Novabiochem AG. Reactions on solid support were carried out in arrays of disposable polypropylene columns (20 mL, "Econo-Pac™ columns") from Bio-Rad Laboratories GmbH. These columns were vortexed with a mechanical shaker (IKA-Vibrax™ VXR, IKA Labortechnik GmbH) and connected *via* polypropylene tubing to an evacuable filtering flask. The columns were closed with septa and reagents were added through a needle with a syringe or a pipette (Finnpipette digital™, Labsystems Oy.).

Preparation of resin-bound (3-oxobutyryl)piperazine 1. To a suspension of Wang resin (45.0 g, 42.3 mmol) in dichloromethane (DCM, 600 mL) first pyridine (52 mL) and then a solution of 4-nitrophenyl chloroformate (43.0 g, 231 mmol) in DCM (200 mL) were added. After stirring for 3 h at room temperature the mixture was filtered, the resin was washed with DCM (5 x 300 mL) and then added to a cold solution of

piperazine (38.2 g, 444 mmol) in DMF (600 mL). The resulting mixture was stirred for 13 h, filtered and the resin was washed extensively with DMF, DCM and methanol. After drying, approx. 45 g of resin-bound piperazine was obtained.

To a suspension of this resin (0.60 g, approx. 0.6 mmol) in DMF (4 mL) a freshly prepared solution of 3-oxobutyric acid phenyl ester[7] (5 equivalents, prepared by refluxing a solution of phenol and 2,2,6-trimethyl-1,3-dioxin-4-one in toluene for 1 h and used without isolation) in toluene (6 mL) was added, followed by the addition of diisopropylethylamine (2 mL). The resulting mixture was shaken for 2 h, filtered, the resin was washed with DMF and the acylation was then repeated once as described above for 3 h. Washing with DMF yielded the resin-bound (3-oxobutyryl)piperazine **1**, which was used for the following reactions without drying.

General procedure for the solid-phase synthesis of 1H-1,2,3-triazole-4-carboxylic acid amides. To the resin-bound 3-oxobutyramide **1** (prepared as described above from 0.60 g of resin-bound piperazine; approx. 0.6 mmol) a solution of the primary amine (3.0 mmol) in DMF (4 mL) was added, followed by the addition of triethyl orthoformate (4 mL). The resulting mixture was shaken for 24 h and then filtered. The resin was washed with DMF (2 x 10 mL) and then a solution of *p*-toluenesulfonyl azide (0.60 mL, 3.84 mmol) in DMF (6 mL) was added to the resin, followed by the addition of diisopropylethylamine (2 mL). After shaking for 24 h the mixture was filtered and carefully washed with DMF, methanol, DCM and 10% AcOH in DCM. It was then suspended in a solution of 60% TFA in DCM (8 mL) and shaken for 3 h. Filtration, washing with DCM and concentration of the combined filtrates gave the crude triazoles **4a-c** as oils.

[5-Methyl-4-(piperazine-1-carbonyl)-1H-1,2,3-triazol-1-yl]acetic acid benzyl ester trifluoroacetate (**4a**). HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 13.3 min, 65% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 3.20 (m, 4H), 3.82 (m, 2H), 4.18 (m, 2H), 5.21 (s, 2H), 5.57 (s, 2H), 7.39 (s, br, 5H), 8.99 (s, br, 2H). For analytical purposes, this compound was derivatized by conversion into the corresponding 2-tolylurea by reaction with 2-methylphenyl isocyanate. The triazole obtained from 0.60 g of starting Wang resin gave 201 mg (70%) of the 2-tolylurea. Colourless solid, m.p. 125-127 °C (AcOEt). Anal. Calcd. for $C_{25}H_{28}N_6O_4$ (476.53): C, 63.01; H, 5.92; N, 17.64. Found: C, 62.93; H, 6.06; N, 17.10.

[1-(4-Methoxybenzyl)-5-methyl-1H-1,2,3-triazol-4-yl]piperazin-1-ylmethanone trifluoroacetate (**4b**). HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 10.3 min, 52% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.20 (m, 4H), 3.72 (s, 3H), 3.80 (m, 2H), 4.17 (m, 2H), 5.55 (s, 2H), 6.92 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 8.93 (s, br, 2H). For analytical purposes, this compound was derivatized by conversion into the corresponding 4-chlorophenylurea by reaction with 4-chlorophenyl isocyanate. The triazole obtained from 1.20 g of starting Wang resin gave 190 mg (34%) of the 4-chlorophenylurea. Colourless solid, m.p. 202-204 °C (AcOEt). Anal. Calcd. for $C_{23}H_{25}ClN_6O_3$ (468.94): C, 58.91; H, 5.37; N, 17.92. Found: C, 59.03; H, 5.45; N, 17.72.

{5-Methyl-1-[2-(4-nitrophenyl)ethyl]-1H-1,2,3-triazol-4-yl}piperazin-1-ylmethanone trifluoroacetate (**4c**). Yield of crude trifluoroacetate: 75%. HPLC (Lichrosorb RP 18, acetonitrile/water gradient, monitoring at 254 nm): elution at 14.6 min, 82% pure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.37 (s, 3H), 3.15 (m, 4H), 3.30 (t, J

= 7.0 Hz, 2H), 3.82 (m, 2H), 4.15 (m, 2H), 4.64 (t, J = 7.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 8.13 (d, J = 8.0 Hz, 2H), 9.01 (s, br, 2H). For analytical purposes, this compound was derivatized by conversion into the corresponding acetamide by reaction with acetic anhydride. The resulting product was identical to the compound obtained from 1-acetylpiperazine by acetoacetylation,[7] condensation with 2-[4-(nitrophenyl)]ethylamine and cyclization by treatment with *p*-toluenesulfonyl azide and triethylamine. Colourless solid, m.p. 142-144 °C (AcOEt). Anal. Calcd. for $C_{18}H_{22}N_6O_4$ (386.41): C, 55.95; H, 5.74; N, 21.74. Found: C, 56.13; H, 5.93; N, 21.28.

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