Preparation of Spiropiperidines in Water

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

An environmentally benign spirocyclization is described for the synthesis of 4-spiropiperidines from 2-aminocarbohydrazides in water at room temperature without any catalyst. The condensation of carbocyclic 2-aminocarbohydrazides with N-benzylpiperidinone (2) led to 3′-aminospiropiperidine-quinazolinones (3a-3d). Anthranilic hydrazide 4 gave 2-amino-N′-(1-benzylpiperidin-4-ylidene)benzohydrazide (7), while glycine hydrazide (8) reacted with 2 moles of 2 to afford 1-benzylpiperidin-4-ylidenamino-1,4,8-triazaspiro[4.5]decane (9). All products precipitated from the reaction mixture and were obtained in excellent yields. No further work-up or purification was necessary.

Keywords: Spirocyclization, spiropiperidines, spiroquazolinones, green synthesis, aqueous media, methylene-bridged quazolinones

1. Introduction

The piperidine ring is a common heterocyclic unit in many alkaloids, and is a key moiety in numerous drug candidates. A number of 4-spiropiperidines have been reported to possess biological and pharmaceutical activities.¹⁻³ Spiroyclic carbamate A (Figure 1) has been tested as a novel, highly selective⁴ nitric oxide synthase inhibitor. Spiropiperidine-quinazoline B and its derivatives are used to treat inflammatory disease and pain.⁵ As a ligand of the nociceptin receptor, cis-spiropiperidine C exhibits a 20-fold higher affinity than that of its trans stereoisomer.⁶ 4-Oxaimidazolidine heterocycle D has been used as an antagonist against addiction to narcotic analgesics,⁷ while

Figure 1.
some 1,4,8-triaza[4.5]decan-2-ones display a high inhibitory index against the B-16 melanoma cell line. Moreover, compounds with a 3N-aminoquinazoline motif demonstrate interesting activities. Substituted aminoquinazolinethione E, for instance, exerts excellent insecticidal activity against greenhouse whitefly, and quinazolinedione F exhibits inhibitory activity against haematopoietic prostaglandin D2 synthase. 3

4-one triazocinoquinazolinones and 2-alkyl/aryl quinazolinones are key intermediates for the synthesis of naphthofused 1,4,5-oxadiazepinoquinazolinones, biologically active Schiff bases, triazocinoquinazolinones and 2-alkylaryl quinazolinones.

Kouznetsov et al. reported that a four-step synthetic route from commercially available 1-benzyl-4-piperidinone and anilines provided an efficient preparation of spiro[piperidine-4,2'-1H]quinolines. Spiro[1,2,4-benzotriazine-3(4H),4'-1H-substituted]-piperidines were obtained through the air oxidation of 2-aminomethylenehydrazones of N-benzylpiperidines. The effect of microwave irradiation on the formation of the spiroimidazoquinazoline was investigated by Feliu et al. As compared with conventional heating, the microwave-assisted solid-phase synthesis of 1,4,8-triaza[4.5]decan-2-one derivatives from 1-benzyl-piperidin-4-one (2) and an α-amino acid amide was significantly improved. Spirocyclization of 1-acetyl-4-piperidone with 1,2-diamino-2-methylpropane in refluxing benzene gave 8-acetyl-2,2-dimethyl-1,4,8-triaza[4.5]decan-2-one.

We already developed a method by which diendo-and diexo-3-aminonorbornene(ene)-2-carbohydrazides (1a-1d) were applied to form heterocycles. Refluxing of the above hydrazides with γ-oxoacid or γ-ketoester in toluene yielded methylene-bridged phthalazino[1,2-b]quinazolinones or cyclopenta[5,6]pyridazino[6,1-b]quinazolinones.

Our present aim was to expand the possibilities through the condensation of 1a-1d with 1-benzylpiperidin-4-one (2). The target of this project was to prepare methylene-bridged spiropiperidines. Moreover, the chemical and stereochemical features of these saturated and partially saturated heterocycles, like those of their aromatic analogues, should be of importance from pharmacological aspects. To diendo-3-aminobicyclo[2.2.1]heptane-2-carbohydrazide 1a, or diendo-3-aminobicyclo[2.2.1]hept-5-ene-2-carbohydrazide 1b, or diexo-3-aminobicyclo[2.2.1]-heptane-2-carbohydrazide 1c, or diexo-3-aminobicyclo[2.2.1]-hept-5-ene-2-carbohydrazide 1d dissolved in water, N-benzylpiperidin-4-one was added dropwise. During stirring at room temperature, in about 10 min spiropiperidine derivatives 3a-3d started to precipitate.

Only a few reports describe the spirocyclization of anthranilyldrazide 4 with cycloalkanones. 3'-Amino-1', 2'-dihydrosipropyl[cyclohexane-1,2'-quinazolin]-4'(3'H)-one 6 was formed when 4 was refluxed with cyclohexanone 5 in acetic acid or in ethanol. It is important to note that a 3-cyclohexyldenaminoo derivative was obtained on the condensation of 4 and 2 or more equivalents of cyclohexanone.

On analogy with the synthesis of 3a-3d, we attempted to prepare their aromatic derivatives. The condensation of anthranilic hydrazide 4 with 2 gave only the hydrazone 7 in high yield. This can be explained by the less nucleophilic character of the aromatic amine.

To investigate the limit of spirocyclization in water, we decided to explore the above-mentioned strategies in

![Scheme 1.](image-url)

**Scheme 1.**

**2. Results and Discussion**

We turned our attention to a greener and sustainable approach for the preparation of an N-benzylpiperidine derivative of 2',2''-disubstituted spiroquinazolinones. The use of water as a solvent for organic transformations offers numerous environmental benefits. In many reactions, a significant rate enhancement is observed in water relative to organic solvents. Water was found to be an ideal solvent for the multicomponent synthesis of heterocycles, for the preparation of 2-pyrrolecarbaldimines, and pyrazoles and diazepines.
the reaction of glycine hydrazide\textsuperscript{40} 8 and 2; again, a crystalline product was precipitated in moderate yield (Scheme 3). The product was not an 1-amino-8-benzyl-2-oxo-1,4,8-triazaspiro[4.5]decane, but its benzylpiperidin-4-yldenamino analogue 9, which was formed by the condensation of 8 with 2 moles of 2. When the reaction was repeated with 2 moles of 2 the yield of 9 increased to 87%.

During the cyclization, aminobicycloalkane(ene) carbohydrazide 1a-1d retained their configurations in all cases. The constitutions of the compounds were proved via their IR and NMR spectra. The IR spectra of 3b and 3d, with a norbornene skeleton, exhibit a characteristic absorption bands in the regions 3080–3050 cm\(^{-1}\) (\(\nu_{=CH}\)) and 745–697 cm\(^{-1}\) (\(\delta_{=CH}\)). The position of the latter band is governed by the stereochemical features of the spiroquinoxazinones: in the IR spectra of the exo isomer, this band is in a lower interval (702 cm\(^{-1}\)) than for the endo stereoisomer (734 cm\(^{-1}\))\textsuperscript{45}. The presumed \textit{diendo} and \textit{diexo} configurations of the spirotricyclic compounds 3a, 3b and 3c, 3d were proved by \(^1\text{H}-\text{NMR}\) spectroscopy. For 3a and 3b, the \textit{diendo} annellation of the norbornene moiety is revealed by the splittings\textsuperscript{46}. On \textit{diexo} annellation, 4’a-H exhibits a \(dd\) split, proved by the value of \(\sim 4\) Hz\textsuperscript{47} for the 4’a-5’ H–H coupling. The \textit{diexo} annellation of the norbornene(ene) to the perhydropyrimidinone in 3c and 3d follows from the \(d\) split of 4’a-H, which is a doublet due to the coupling with 8’a-H (split by \(\sim 7.5\) Hz). Each of the spiro compounds 3a-3d and 9 gave a \(^{13}\text{C}\) signal for a quaternary C-2’ at 73–79 ppm. This chemical shift appears reasonable for an –NHCR\(_2\)NH– system, where R is an alkyl group\textsuperscript{48}. The formation of 3’-amino-substituted compounds was confirmed by the appearances of NH\(_2\) signals in the \(^1\text{H}-\text{NMR}\) spectra (4.06–4.51 ppm) and the lack of two NH groups in IR.

3. Conclusion

In conclusion, a green approach has been demonstrated for the preparation of synthetically and pharmaceutically relevant spiropiperidines. The condensations of 3-aminonorborane(ene)-2-hydrazides (1a-1d) with 1-benzylpiperidin-4-one (2) gave 3’-amino-substituted spiro[piperidine-4,2’-quinazolinones] 3a-3d, while from less nucleophilic anthranilic hydrazide (4) a hydrazone 7 was formed. It was somewhat surprising that in the reaction of glycine hydrazide with 1-benzylpiperidin-4-one only a double condensed 1,4,8-triazaspiro[4.5]decane derivative 9 was obtained. At ambient temperature, all these reactions were complete in 12 h in water without the need for any catalyst. This method includes some important as-
sects, such as the use of water as a green solvent and mild reaction conditions.

4. Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. $^1$H-NMR (400 Hz) and $^{13}$C-NMR (100 MHz) spectra were recorded on a Bruker Avance DRX 400 spectrometer, with TMS as internal reference and DMSO-$d_6$ or CDCl$_3$ as solvent. FT-IR spectra recordings were performed on a Perkin-Elmer 100 FT-IR spectrometer. Elemental analysis was carried out on a Perkin-Elmer 2400 elemental analyser.

Preparation of $\textit{dieno-}$ and $\textit{dieno-3'}$-$\textit{amino-1-benzyl-5',8',8''-methano-4'a,5',6',7',8',8''-a-hexahydrospiro[piperidine-4,2'(1'H)-quinazolin]}$-$4'(3'H)$-one (3a–3d).

To a stirred solution of hydrazides 1a–1d (5.0 mmol) in 10 mL of water, 0.95 g (5.0 mmol) of 1-benzyl-4-piperidinone (2) was added in portions at room temperature. After vigorous stirring for 12 h, products 3a–3d precipitated. The precipitates of 3a–3d were filtered off, washed with water (15 mL), and dried upon a porous plate at 100 °C.

$\textit{dieno-3'}$-$\textit{Amino-1-benzyl-5',8'-methano-4'a,5',6',7',8',8''-a-hexahydrospiro[piperidine-4,2'(1'H)-quinazolin]}$-$4'(3'H)$-one (3a). Yield: 97%; colourless powder; m.p.: 202–204 °C (H$_2$O); IR (KBr, cm$^{-1}$): 3437 (NH), 3334, 3311 (NH$_2$), 1623 (C=O), 1587 (C=O); $^1$H-NMR (CDCl$_3$): $\delta$ 1.20–1.61 (8H, m, 2-6-H, 1'-NH, 6'-H, 7'-H, 9'-H) 1.72 (1H, dd, $J = 3.0$, 13.5 Hz, 9'-H), 2.05 (1H, dd, $J = 4.1$, 8.8 Hz, 4''-a-H), 2.24–2.46 (3H, m, 2-6-H), 2.50 (1H, s, 8'-H), 2.65-2.88 (4H, m, 2-6-H, 5'-H), 3.47 (1H, br s, 8'a-H), 3.54 (2H, s, benzyl CH$_2$), 4.17 (2H, s, NH$_2$), 7.18–7.37 (5H, m, Ar-H); $^{13}$C-NMR (CDCl$_3$): $\delta$ 21.4, 23.0, 30.4, 35.0, 37.2, 40.0, 40.8, 45.2, 49.1, 49.5, 50.0, 62.3, 74.2, 126.6, 127.8 (2xCH), 128.6 (2xCH) 138.5, 170.5; Anal. calc. for C$_{20}$H$_{26}$N$_4$O (%) C, 70.56; H, 8.29, N, 16.46. Found: C, 70.25; H, 8.48; N, 16.30; m/z [M+H]$^+$ 341.2.

$\textit{dieno-3'}$-$\textit{Amino-1-benzyl-5',8'-methano-4'a,5',6',7',8',8''-a-tetrahydropyrido[piperidine-4,2'(1'H)-quinazolin]}$-$4'(3'H)$-one (3b). Yield: 94%; colourless powder; m.p.: 162–164 °C (H$_2$O); IR (KBr, cm$^{-1}$): 3426 (NH), 3319, 3311 (NH$_2$), 3062 (v$_{CH}$), 1622 (C=O), 1586 (C=O), 702 (v$_{NH}$); $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.22 (1H, d, $J = 9.6$ Hz, 9'-H), 1.38–1.81 (4H, m, 9'-H, 2-6-H and 1'-NH), 1.86 (1H, d, $J = 7.5$ Hz, 4''-a-H), 1.96–2.61 (6H, m, 2-6-H), 2.68 (1H, s, 8'-H), 2.92 (1H, t, $J = 8.2$ Hz, 8''-a-H), 3.16 (2H, s, benzyl CH$_2$), 4.51 (2H, s, NH$_2$), 6.11 (1H, dd, $J = 2.9$ Hz, $J = 5.7$ Hz, 7'-H), 6.22 (1H, dd, $J = 2.8$ Hz, $J = 5.6$ Hz, 6'-H), 7.16–7.33 (5H, m, Ar-H); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 30.0, 33.8, 43.4, 43.8, 45.4, 47.4, 49.0, 49.3, 50.8, 61.9, 73.1, 126.7, 128.1 (2xCH), 128.6 (2xCH) 135.5, 138.3, 138.8, 168.6; Anal. calc. for C$_{29}$H$_{36}$N$_4$O (%) C, 70.98; H, 7.74; N, 16.55. Found: C, 70.75; H, 7.96; N, 16.21; m/z [M+H]$^+$ e339.2.

Preparation of 2-amino-$'N'$-(1-benzylpiperidin-4-ylidene)benzohydrazide (7). To a stirred solution of anthranilic hydrazide (4) (0.76 g, 5.0 mmol) in 15 mL of water, 0.95 g (5.0 mmol) of 1-benzyl-4-piperidinone (2) was added in portions at room temperature. After vigorous stirring for 12 h, product 7 precipitated. The precipitate of 7 was filtered off, washed with water (15 mL), and dried upon a porous plate at 100 °C.

Yield: 91%; colourless needles; m.p.: 165–167 °C (H$_2$O); IR (KBr, cm$^{-1}$): 3438, 3296 (NH$_2$), 3229 (NHCO), 1622 (C=O), 1586 (C=O), 756 (Ar$_{CH}$); $^1$H-NMR (DMSO-$d_6$): $\delta$ 2.35–2.49 (6H, m, cycloalkyl CH$_3$), 2.52–2.58 (2H, m, cycloalkyl CH$_2$), 3.54 (2H, s, benzyl CH$_2$), 6.15 (2H, br s, NH$_2$), 6.48–7.48 (9H, m, Ar-H), 10.41 (1H, s, NHCO); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 28.9, 35.3, 52.9, 54.0,
62.2, 115.5, 117.0, 127.8 (2xC), 129.1 (2xC), 129.6 (4x C), 139.2, 150.3, 162.1, 166.1; Anal. calcld. for C_{26}H_{33}N_{5}O (%) : C, 70.78; H, 6.88; N, 17.38. Found: C, 70.59; H, 6.91; N, 17.21.

1-(Benzylpiperidin-4-ylidenamino)-8-benzyl-2-oxo-1,4,8-triazaspiro[4.5]decane (9). To a stirred solution of glycine hydrazide (8) (0.45 g, 5.0 mmol) in 10 mL of water, 0.95 g (5.0 mmol) or 1.89 g (10.0 mmol) of 1-benzyl-4-piperidinone (2) was added in portions at room temperature. After vigorous stirring for 12 h, product 9 precipitated. The precipitate 9 was filtered off, washed with water (10 mL), and dried upon a porous plate at 100 °C.

Yield: 45% or 87% (based on hydrazide 8); colourless powder; m.p.: 141–143 °C (H₂O); IR (KBr, cm⁻¹): 3285 (NH), 1685 (C=O), 1637 (C=N); ¹H-NMR (DMSO-δ): δ 1.43–2.76 (16H, m 2-6-H), 3.02 (1H, t, J = 9.3 Hz, 4-NH), 3.25 (2H, d, J = 9.2 Hz 3-H), 3.47 (2H, s, benzyl-H), 3.55 (2H, s, benzyl-H), 7.20–7.37 (10H, m, Ar-H); ¹³C-NMR (DMSO-δ): δ 31.4, 33.4 (2xC), 35.4, 47.5, 50.2 (2xC), 53.3, 54.1, 61.9, 62.8, 78.4, 127.7, 127.8, 129.0 (2xC), 129.1 (2xC), 129.5 (2xC), 129.6 (2xC) 139.2, 139.5, 167.9, 174.6; Anal. calcld. for C_{26}H_{33}N_{5}O (%): C, 72.36; H, 7.71; N, 16.23. Found: C, 72.55; H, 7.98; N, 16.01; m/z [M+H]+ 432.2.

5. Acknowledgements

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6. References

Povzetek
Opisana je okolju prijazna nekatalizirana spirociklizacija za pripravo 4-spiropiperidinov iz 2-aminokarbohidrazidov v vodi kot topilu. Kondenzacije karbocikličnih 2-aminokarbohidrazidov z N-benzilpiperidinonom so vodile do 3’-ami nospiropiperidine-kinazolinonov, antranilhidrazid je dal 2-amino- N’-(1-benzilpiperidin-4-iliden)benzohidrazid, medtem ko je glicinhidrazid regiral z dvema ekvivalentoma N-benzilpiperidinona do ustreznega -benzilpiperidin-4-ilidena-mimo-1,4,8-triazaspiro[4,5]dekana. Vsi produkti so bili enostavno izolirani s filtracijo z odličnimi izkoristki in čistočo.