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ABSTRACT

The synthesis of two enantiomeric pairs of pyrimidoisoindolones 9a, 9b and 10a, 10b is reported. During a domino ring-closure reaction, followed by cycloreversion, the chirality of diendo-(−)-(1R,2S,3R,4S)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide ([−]-1) was successfully transferred to heterocycles (+)-9a, (+)-10a, (−)-9b, (−)-10b and (−)-10c.

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1. Introduction

Several pyrimido[2,1-a]isoindoles are well known for their potential biological and pharmacological properties such as pro-lactin-inhibition, antidepressant and diuretic, anticipodal, antifungal activity. In contrast to these findings, derivatives of these heterocycles are still insufficiently studied, even less their enantiomers. To our best knowledge so far, as single enantiomers, several pyrimidoisoindole derivatives have been synthesized. Compounds were prepared by the application of retro Diels–Alder (rDA) reaction.9

2. Results and discussion

In an earlier paper, we described an enantioselective synthesis of pyrimido[2,1-a]isoindoles by microwave-induced retro Diels–Alder reaction. dixo-(−)-(3)-Amino-norbornene-2-carboxylic acid readily available through an enzymatic resolution was used as a starting chiral source.11

The goal of the present work was to explore further extensions of the above methodology that includes (i) the introduction of diendo-(−)-(ethyl-3-aminonorbornene-2-carboxylate as a chiral source, (ii) the use of 2-formyl-, 2-acetly- and 2-(4-methylbenzoyl)-benzoic acid for the preparation of isoindoloquinazolinone intermediates, (iii) the investigation of the steric effect of the 2-formyl and 2-acetyl groups on the diastereoselectivity of the ring-closure reaction, (iv) separation of diastereomers, and (v) removal of cyclopentadiene in a retro Diels–Alder reaction to obtain pyrimido[2,1-a]isoindolone racemates and enantiomers.

Both racemic and enantiomeric diendo-3-aminobenzonorbornene-2-carboxyamide for the synthesis of isoindolo-quinazolines were prepared by a known literature protocol. A preparative-scale resolution of racemic ethyl diendo-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylates was achieved by adopting the diastereomeric salt formation with (R)-(−)-mandelic acid. The reaction afforded ethyl (−)-(1R,2S,3R,4S)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate applied in the synthesis of (−)-(1R,2S,3R,4S)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide (−)-1.

In preliminary studies on the three-step domino reaction, racemic diendo-3-aminobenzonorbornene-2-carboxamide (±)-1 was reacted with 2-formylbenzoic acid (R = H), 2-acetlybenzoic acid (R = Me) or 2-(4-methylbenzoyl)benzoic acid (R = 4-MeC 6H 4) in toluene under reflux in the presence of p-toluensulfonylic acid (p-TSA) as catalyst. The reaction mixture of (±)-1 (monitored by TLC) was transferred to a neutral Al 2O 3 column and the cyclization products (±)-2a–4b were eluted with EtOAc. The solvent was then removed and diastereomeric ratios of (±)-2a–4a and (±)-2b–4b were determined by the integration of 1H NMR spectra. The diastereomically pure isoindoloquinazolinone were readily separated by silica gel chromatography. The structures of (±)-2a, (±)-2b, (±)-3a and (±)-3b were elucidated on the basis of spectroscopic data, in particular, information acquired by 2D-NMR (Scheme 1). The relative configurations of diastereomeric pairs (±)-2a and (±)-2b as well as (±)-3a and (±)-3b were determined by employing X-ray crystallographic analysis (Fig. 1).

(±)-4a was supported by a strong NOE measured between ArH-2,6 and 3-H (olefinic) atoms.16

With the isoindoloquinazolinones in hand, considerable efforts were made to accomplish their thermal decomposition under microwave irradiation. On the basis of the optimized reaction conditions shown in Scheme 1, pyrimidoisoindoles (±)-5a–5c were obtained almost quantitatively and in high purity from both 2a–4a and 2b–4b. Interestingly, in our earlier study,17 (±)-5a formed directly on cyclization and thermolysis through the reaction of diexo-3-amino-7-oxanorbornene-2-carboxamide with 2-formylbenzoic acid, when the non-isolated oxygen-bridged intermediate decomposed via the loss of furan in a retro Diels–Alder reaction.

To establish the generality and synthetic potential of the cyclization of (±)-1 with 2-formylbenzoic acid or 4-oxo acids followed by the easy separation of the diastereomers and the successful retro Diels–Alder reaction, the preparation of enantiomerically pure pyrimidoisoindoles (+)-9a and (+)-10a, (−)-9b, and (−)-10b and (−)-10c.

4. Experimental

4.1. General

Melting points were determined on a Kofer apparatus and are uncorrected. 1H NMR (400 Hz) and 13C NMR (100 MHz) spectra were recorded on a Bruker Avance DRX 400 spectrometer, with TMS as internal reference and DMSO-d6 or CDCl3 as solvent. FTIR spectra were recorded on a Perkin-Elmer 100 FT-IR spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyser. Microwave-promoted reactions were performed in sealed reaction vials (10 mL) by means of a CEM, Discover microwave reactor. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. Mass spectra were recorded on a Finnigan MAT 95S spectrometer.

The ee values of (+)-10a and (−)-10b were determined on a Chiralpak IA column (4.6 x 250 mm); detection at 332 nm; eluent: n-hexane/Et2NH/i-PA (75/0.1/25); flow rate: 0.5 mL/min; retention times (min) for (+)-10a: 23.96 (antipode, (−)-10b: 25.66. Conditions for (+)-11a and (−)-11b: Chiralpak IA column (4.6 x 250 mm); detection at 236 nm; eluent: n-hexane/Et2NH/i-PA (90/0.1/10); flow rate: 0.5 mL/min; retention times (min) for (+)-11a: 41.26 (antipode, (−)-11b: 46.02. Data for (+)-9a and (−)-9b: Chiralpak IA column (4.6 x 250 mm); detection at 220 nm; eluent: n-hexane/Et2NH/i-PA (90/0.1/10); flow rate: 0.5 mL/min; retention times (min) for (+)-9a: 49.19 (antipode, (−)-9b: 51.57. The ee value of (±)-1 was determined on a GC equipped with a Chrompack Chirasil-Dex CB column after a simple derivatization with Ac2O in the presence of 4-dimethylaminopyridine and pyridine [120 °C for 4 min → 170 °C (temperature rise 10 °C/min); 140 kPa; retention times (min), (±)-1: 22.25 (antipode: 23.25)].

3. Conclusions

In conclusion, an efficient synthesis of pyrimidoisoindole enantiomers has been accomplished. The chirality of parent β-amino carboxamide (−)-1 was completely preserved during the stereo-controlled three-step domino reaction to give epimeric pairs. The effective separation of diastereomers followed by their racemization-free retro Diels–Alder reaction allowed the formation of enantiomerically pure pyrimidoisoindoles (±)-9a and (±)-10a, (±)-9b, and (±)-10b and (±)-10c.

![Scheme 1. Preparation of pyrimidoisoindoles (±)-5a–5c by domino ring closure, followed by thermal cycloreversion.](http://dx.doi.org/10.1016/j.tetasy.2017.07.006)
II diffractometer using Cu Kα (λ = 1.54184 Å) or Mo Kα (λ = 0.71073) radiation. The CrysAlisPro\textsuperscript{18} or Denzo-Scalepack\textsuperscript{19} program packages were used for cell refinements and data reductions. Multi-scan absorption corrections (CrysAlisPro\textsuperscript{18} or SADABS\textsuperscript{20}) were applied to the intensities before structure solution. The structures were solved by charge flipping method using the SUPERFLIP\textsuperscript{21} software. Structural refinements were carried out using SHELXL-2014.\textsuperscript{22} The high R-values and residual densities in 3a are due to the low data quality and possible twinning. However, not satisfactory twin model could be found and therefore no twin model was used in the final refinement. In 2b and 3b the NH hydrogen atoms were located from the difference Fourier map and refined isotropically. Other hydrogen atoms were positioned geometrically and constrained to ride on their parent

Figure 1. ORTEP views of diastereomeric pairs 2a–2b and 3a–3b.

Scheme 2. Synthesis of antipode pairs [[(+)-9a–(−)-9b] and [[(+)-10a–(−)-10b]] and single enantiomeric pyrimidoisoindoles.
4.1. (15′SR,4′AR,4′AS,6′AR,12′RA)′-1,4,4a,6,6a,12a-Hexahydro-1,4-methanoido[2,1-q]quinazoline-5,11-dione (5-d)-2a

Yield: 24%, colourless crystals, mp 302–304 °C (EtOH). IR (KBr): 3218, 3112, 3062, 2969, 1683, 1665, 1470, 1398, 737 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 1.45 (1H, d, J = 8.8 Hz, H-13), 1.62 (1H, d, J = 8.7 Hz, H-13), 2.90 (1H, dd, J = 9.1 Hz, J = 4.1 Hz, H-4a), 3.17 (1H, s, H-4), 3.26 (1H, s, H-1), 5.03 (1H, dd, J = 9.1 Hz, J = 3.5 Hz, H-12a), 5.64 (1H, s, H-6a), 6.38 (1H, d, J = 5.8 Hz, J = 2.8 Hz, H-2), 6.42 (1H, dd, J = 5.7 Hz, J = 2.8 Hz, H-3), 7.53–7.79 (4H, m, H-Ar), 8.81 (1H, s, CONH). ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm) 42.1, 47.2, 48.8, 49.3, 51.1, 66.1, 123.8, 124.5, 130.4, 131.5, 133.0, 136.6, 143.3, 167.2, 171.5. Anal. calcd. for C₁₆H₁₄N₂O₂ (%): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.65; H, 5.95; N, 10.65. MS: (ESI) m/z = 267.32 [M+H⁺].

4.2. (15′SR,4′AR,4′AS,6′AR,12′RA)′-1,4,4a,6,6a,12a-Hexahydro-1,4-methanoido[2,1-q]quinazoline-5,11-dione (5-d)-2b

Yield: 49%, colourless crystals, mp 262–266 °C (EtOH). IR (KBr): 3246, 3165, 3064, 3104, 2970, 2930, 2890, 1707, 1683, 1666, 1655, 1468, 1383, 737 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 1.46 (2H, m, H-13), 3.03 (1H, dd, J = 8.8 Hz, J = 4.1 Hz, H-4a), 3.26 (1H, s, H-4), 3.60 (1H, d, J = 8.8 Hz, J = 3.6 Hz, H-12a), 5.80 (1H, s, H-6a), 5.95 (1H, dd, J = 6.0 Hz, J = 2.9 Hz, H-2), 6.06 (1H, dd, J = 5.6 Hz, J = 2.7 Hz, H-3), 7.51–7.74 (4H, m, H-Ar), 8.92 (1H, s, CONH). ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm) 44.7, 46.0, 46.1, 52.4, 54.9, 66.7, 123.5, 124.5, 130.3, 135.7, 137.7, 141.5, 165.4, 172.1. Anal. calcd. for C₁₆H₁₄N₂O₂ (%): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.15; H, 5.45; N, 10.45. MS: (ESI) m/z = 201.26 [M+DAH⁺]+ and 267.23 [M+H⁺].

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a) R1 = Σ||Fobs||-|Fcalc||Σ||Fobs||

b) wR2 = [Σ(wR²)]/[Σ(w²)]²]1/2.
4.2.5. \((1S,4R,4aS,6aR,12aR\rangle-6a-(p-Toly)-1,4,4a,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-a]quinazoline-5,11-dione (±)-4a)

Yield: 3%, colourless crystals, mp 230–232 °C (EtOAc). IR (KBr): 3291, 3075, 3018, 2986, 2944, 2904, 1756, 1676, 1652, 1111, 1487, 1355, 1322, 738 cm⁻¹. 1H NMR (400 MHz, DMSO-d₆) δ (ppm) 1.38 (2H, m, H-13), 2.26 (3H, s, CH₃), 2.34 (1H, dd, J = 8.8 Hz, J = 3.9 Hz, H-4a), 2.94 (1H, d, J = 10.3 Hz, CONH), 3.04 (1H, s, H-4), 3.20 (1H, H-1), 3.79 (1H, m, H-12a), 6.16 (1H, dd, J = 5.6 Hz, J = 2.9 Hz, H-2), 6.23 (1H, dd, J = 5.6 Hz, J = 2.8 Hz, H-3), 7.5–7.77 (8H, m, H-Ar). 13C NMR (100 MHz, DMSO-d₆) δ (ppm) 21.4, 46.3, 46.5, 46.7, 57.6, 73.9, 124.5, 125.2, 126.2 (2C), 128.7, 130.5, 130.9 (2C), 135.4, 135.5, 138.5, 138.9, 139.4, 163.5, 170.7. Anal. calc. for C₁₈H₁₄N₂O₂ (%): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.12; H, 5.75; N, 7.75. MS: (ESI) m/z = 291.39 [M+H]+ and 357.26 [M+H]+.

4.2.6. \((1S,4R,4aS,6aS,12aR\rangle-6a-(p-Toly)-1,4,4a,6a,12a-hexahydro-1,4-methanoisoindolo[2,1-a]quinazoline-5,11-dione (±)-4b)

Yield: 39%, colourless crystals, mp 265–267 °C (EtOAc) (lit. mp 270–271 °C). The NMR spectrum was identical to that of an authentic sample.

4.3. Synthesis of pyrimido[2,1-a]isoindole (±)-5a, (±)-5b and (±)-5c by microwave-induced retro Diels–Alder reaction

All microwave-mediated reactions were carried out in reaction vials sealed with a Teflon cap. Heterocycles (±)-2a, (±)-2b, (±)-3a, (±)-3b, (±)-4a or (±)-4b (25–100 mg) were placed in a microwave test tube (10 mL) containing a magnetic stirrer and 1,2-DCB (2 mL). The test-tube was placed in the cavity of the CEM Discover microwave reactor. The solutions were irradiated during a period of 15 min at 210 °C (power 250 W). The cooled solution diluted with CHCl₃ (6 mL) was then transferred to a SiO₂ column and eluted with n-hexane–EtOAc (1:1).

4.3.1. 1,10B-Dihydroyprimidino[2,1-a]isoindole-2,6-dione (±)-5a

Yield: 89–95%, colourless crystals, mp 270–272 °C (EtOH) (lit. mp 242–244 °C). Spectroscopic data were identical to that of an authentic sample.

4.3.2. 10B-Methyl-1,10B-dihydroyprimidino[2,1-a]isoindole-2,6-dione (±)-5b

Yield: 91–94%, colourless crystals, mp 202–202 °C (EtOAc–iPr₂O). IR (KBr): 3425, 3178, 3043, 2974, 2899, 1724, 1657, 1617, 1472, 1310, 808 cm⁻¹. 1H NMR (400 MHz, DMSO-d₆) δ (ppm) 1.72 (3H, s, CH₂-10b), 5.64 (1H, d, J = 7.6 Hz, H-2), 7.60–7.93 (5H, m, H-4 and H-Ar), 8.84 (1H, s, CONH). 13C NMR (100 MHz, DMSO-d₆) δ (ppm) 27.7, 74.9, 107.4, 123.7, 125.3, 129.5, 130.9, 133.0, 135.0, 148.3, 164.8, 165.5. Anal. calc. for C₁₉H₁₅N₂O₂ (%): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.62; H, 5.00; N, 9.81; MS: (ESI) m/z = 291.30 [M+H]+.

4.4. Synthesis of (±)-(1R,2S,3R,4S)-3-aminoxyclclo[2.2.1]hept-5-ene-2-carboxamide (–)-1

A mixture of (±)-(1R,2S,3R,4S)-3-norbornene-2-carboxamide (–)-1, (350 mg, 2.3 mmol), 2-formylbenzoic acid, 2-acetylbenzoic acid or 2-(4-methylbenzoyl)benzoic acid (2.5 mmol), and p-TSA (0.03 g) in toluene (25 mL) was refluxed for 16 h. The solution was then evaporated off, the residue was dissolved in EtOAc (10 mL), and the solution was transferred to a neutral Al₂O₃ column and eluted with EtOAc. The residue of the eluates was transferred to a silica gel column and eluted with a mixture of n-hexane–EtOAc (2:1). The 1H NMR spectra for optically active compounds were in accordance with those reported for the racemates.

4.5. Synthesis of isoindolo[2,1-a]quinazolines (–)-6a, (+)-6b, (+)-7a, (–)-7b and (+)-8b enantiomers

4.6.1. \((R)-(+)\)-1,10b-Dihydropyrimido[2,1-a]isoindole-2,6-dione (\(\text{(-)}\)-9a)

Yield: 92%, colourless crystals, mp 265–267 °C (EtOAc–n-hexane). \([\alpha]_D^{25} = +441 \text{ (c 0.11, EtOH)}, \text{ee} \geq 99\%.

4.6.2. \((S)-(\text{(-)})\)-1,10b-Dihydropyrimido[2,1-a]isoindole-2,6-dione (\(\text{(-)}\)-9b)

Yield: 96%, colourless crystals, mp 267–269 °C (EtOAc–n-hexane). \([\alpha]_D^{25} = -428 \text{ (c 0.12, EtOH)}, \text{ee} \geq 99\%.

4.6.3. \((R)-(+)\)-10b-Methyl-1,10b-dihydropyrimido[2,1-a]isoindole-2,6-dione (\(\text{(+)}\)-10a)

Yield: 91%, colourless crystals, mp 201–202 °C (EtOAc–i-Pr₂O). \([\alpha]_D^{25} = +429 \text{ (c 0.11, EtOH)}, \text{ee} \geq 99\%.

4.6.4. \((S)-(\text{(-)})\)-10b-Methyl-1,10b-dihydropyrimido[2,1-a]isoindole-2,6-dione (\(\text{(-)}\)-10b)

Yield: 97%, colourless crystals, mp 199–201 °C (EtOAc–i-Pr₂O). \([\alpha]_D^{25} = -450 \text{ (c 0.17, EtOH)}, \text{ee} \geq 99\%.

4.6.5. \((S)-(\text{(-)})\)-10b-(p-Tolyl)-1,10b-dihydropyrimido[2,1-a]isoindole-2,6-dione (\(\text{(-)}\)-11b)

Yield: 89%, colourless crystals, mp 245–247 °C (i-Pr₂O). \([\alpha]_D^{25} = -21.8 \text{ (c 0.36, EtOH)}, \text{ee} \geq 99\%.

Acknowledgements

We are grateful to the Hungarian Research Foundation (OTKA No. K 115731). The financial support of the GINOP-2.3.2-15-2016-00014 project is acknowledged.

A. Supplementary data

Supplementary data (Copies of the \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.07.006.

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