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Synthesis of 3-substituted 2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-ones by sequential reactions of 2-indolylmethyl acetates with α-amino acids†

Antonella Goggiamani, *[a] Antonio Arcadi, [b] Alessia Ciogli,[a] Martina De Angelis,[a] Stefano Dessalvi,[a] Giancarlo Fabrizi,[a] Federica Iavarone,[cd] Antonia Iazzetti, [cd] Alessio Sferrazza*[ae] and Roberta Zoppoli[a]

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The synthesis of 2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-ones from the sequential reaction of amino acid methyl esters with readily available indole-2-ylmethyl acetates is described. The reaction proceeds *in situ* under basic conditions of highly unstable and reactive 2-alkylideneindolenines followed by Michael-type addition of α-amino acid methyl esters/intramolecular cyclization.

Introduction

The indole nucleus has a central position in organic and medicinal chemistry because it is an important structural motif of many natural and synthetic biologically active compounds.[1] Moreover, *N*-fused indole derivatives display various pharmacological properties including antitumor[2] and tubulin polymerization inhibitory activities.[3] Amongst *N*-fused indole heterocycles, pyrazinoindoles and their congeners attract a great deal of attention due to their application as efficient pharmacophores (Fig. 1).[4] Consequentially, the pyrazinoindole system still triggers organic chemists to develop efficient methodologies for diversity-oriented preparations.[5] In this field, the biological properties of pyrazino[1,2-*a*]indol-1-ones have been explored and a variety of synthetic approaches have been developed.[6] Conversely, the pyrazino[1,2-*a*]indol-4-ones have been less studied. To the best of our knowledge, only one process has been reported *via* stereospecific *N*-acylation of indoles with L-amino acids followed by intramolecular cyclization *via* the Pictet–Spengler reaction.[7]

Then, the synthesis of polysubstituted pyrazino[1,2-*a*]indol-4-one derivatives through straightforward one-pot approaches from easily available building blocks would be particularly significant considering their great potential as molecular scaffolds in drug discovery.

During our studies in the synthesis of heterocyclic compounds,[8] great interest has been devoted to constructing/functionalizing indole and indole-fused polycyclic systems through simple domino processes.[9] Recently, we reported the metal-free synthesis of 2-(aminomethyl), (tosylmethyl), and (aryloxymethyl) indoles **2** starting from readily available 2-

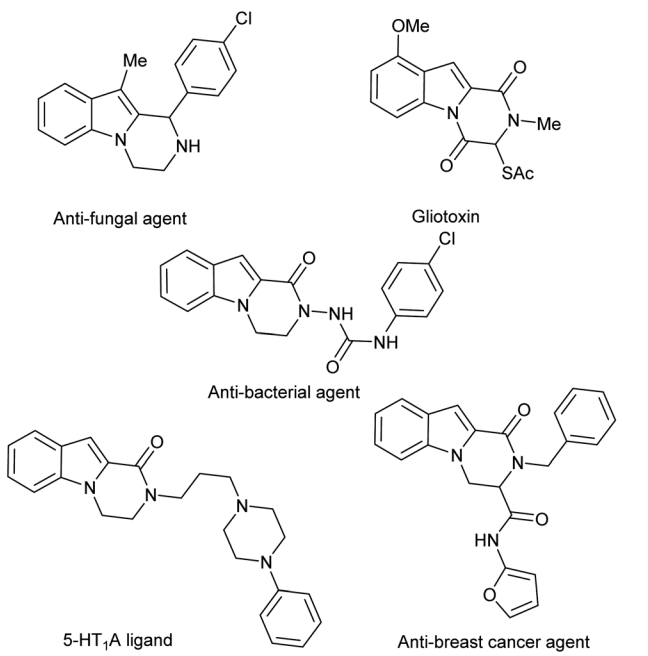

Fig. 1 Biologically active pyrazinoindoles.

[a]*Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza, Università di Roma, P.le A. Moro 5, 00185 Rome, Italy. E-mail: alessia.ciogli@uniroma1.it; m.deangelis@uniroma1.it; stefano.dessalvi@uniroma1.it; giancarlo.fabrizi@uniroms1.it; antonella.goggiamani@uniroma1.it; a.sferrazza@irbm.com; roberta.zoppoli@uniroma1.it*

[b]*Dipartimento di Dipartimento di Scienze Fisiche e Chimiche, Università degli Studi di L'Aquila, Via Vetoio, 67100 Coppito (AQ), Italy. E-mail: antonio.arcadi@univaq.it*

[c]*Dipartimento di Scienze Biotecnologiche di base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, L.go Francesco Vito 1, 00168 Rome, Italy. E-mail: federica.iavarone@unicatt.it; antonia.iazzetti@unicatt.it*

[d]*Policlinico Universitario 'A. Gemelli' Foundation-IRCCS, Rome, 00168, Italy*

[e]*Alessio Sferrazza is currently a research scientist in IRBM S.p.A., Medicinal Chemistry Department, Pomezia, Roma, Italy*

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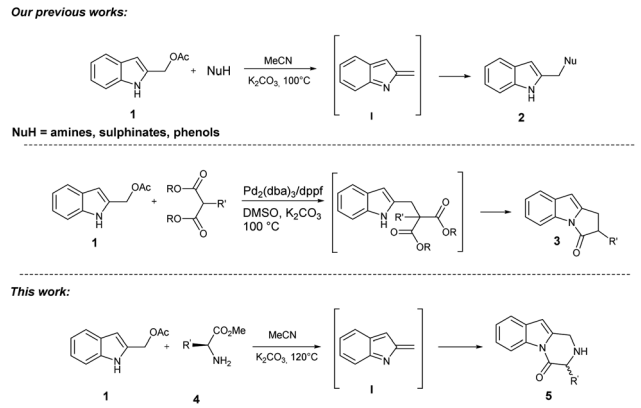
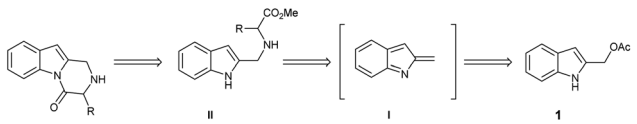


Scheme 1 Our background and this work.



Scheme 2 Retrosynthetic approach to the 2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one scaffold.

indolylmethylacetates **1** and N, O, and S soft nucleophiles. The reaction proceeds through *in situ* generation of highly reactive 2-alkylideneindolenines **I** under basic conditions as provided through ESI-MS and IRMPD spectroscopy analyses.[10] Furthermore, we developed a straightforward assembly of polysubstituted 1,2-dihydro-3*H*-pyrrolo[1,2-*a*]indol-3-ones **3** through a domino palladium-catalyzed reaction of 2-indolylmethylacetates **1** with 1,3-dicarbonyl compounds (Scheme 1).[11]

Based on this background, we envisaged that the reaction of 2-indolylmethyl acetates **1** with α-amino acids **4** should achieve a general entry into the title target **5** through the *in situ* generation of 2-methide-2*H*-indole intermediate **I**/nucleophile Michael addition/cyclization cascade reaction according to the retrosynthetic analysis of Scheme 2.

Herein, we describe the scope and limitations of this approach to the synthesis of multi-substituted 2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one **5**.

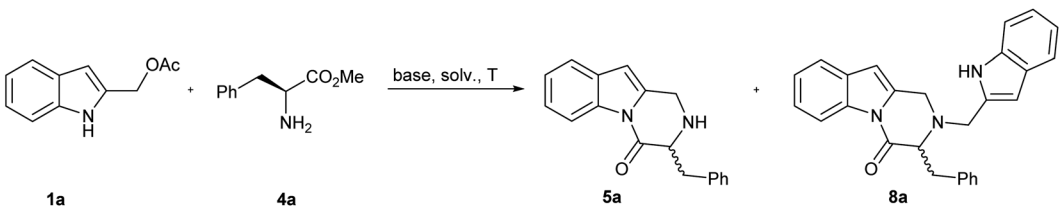
Results and discussion

Indole-2-ylmethyl acetates **1** were obtained with excellent overall yield through the reduction of commercially available ethyl 1*H*-indole-2-carboxylates **6** followed by acetylation: both synthetic steps did not require further purification.[10–12]

For our initial investigations, we examined the reaction of the indole-2-ylmethyl acetates **1a** with two equivalents of methyl L-phenylalaninate **4a** using K_2CO_3 in MeCN at 120 °C (Table 1, entry 1). The reaction proceeded to give the desired 3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one **5a** in 51% yield. A significant side reaction led to the formation of 2-((1*H*-indol-2-yl)methyl)-3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one **8a** in 26% yield. Very likely, the target product **5a** is, also, prone to competitively give an aza-Michael addition on 2-alkylideneindolenine **Ia** to afford **8a** (Scheme 3).

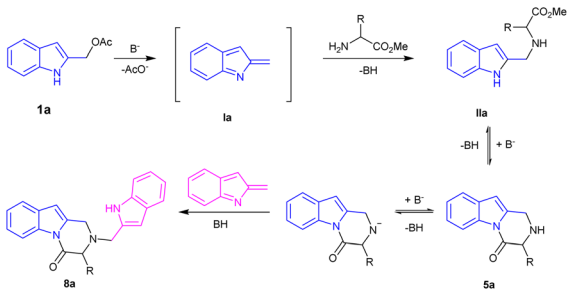
The features of solvent (Table 1, entries 4–6), base (Table 1, entries 8–10), dilution of the reaction mixture (Table 1, entry 3),

Table 1 Optimization studies for the reaction of **1a** with methyl L-phenylalaninate **4a**[a]



Entry[b]	Solvent	*T* (°C)	Base	**4a** (equiv.)	*t* (h)	**5a** (%)	**8a** (%)	**1a** (%)
1	MeCN	120	K_2CO_3	2	23	51	26	—
2[c]	MeCN	170, 150 W	K_2CO_3	2	0.25	54	25	—
3[d]	MeCN	120	K_2CO_3	2	32	34	16	27
4	DMSO	120	K_2CO_3	2	2	30	6	—
5	DMSO	100	K_2CO_3	2	2	37	17	—
6	DMF	120	K_2CO_3	2	0.75	39	20	—
8	MeCN	120	K_3PO_4	2	24	9	5	53
9	MeCN	120	Cs_2CO_3	2	2	36	21	—
10	MeCN	120	Na_2CO_3	2	22	—	—	90
11	MeCN	120	K_2CO_3	3	24	54	20	—
12	MeCN	120	K_2CO_3	4	22	58	14	—
13	MeCN	120	K_2CO_3	5	18	73	8	—

[a] Unless otherwise stated, reactions were carried out on a 0.404 mmol scale using 2 equiv. of base in 3.0 mL of solvent. [b] Yields are given for isolated products. [c] Under microwave irradiation. [d] The reaction was carried out in 9.0 mL of solvent.



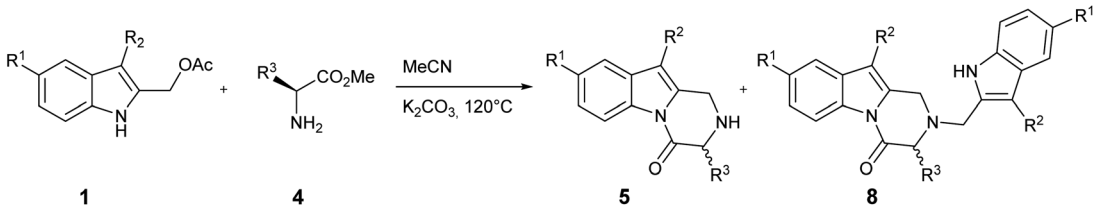
Scheme 3 Competitive formation of **8a**.

and microwave irradiation (Table 1, entry 2) didn't influence the ratio **5a**/**8a**. However, the wished **5a** was isolated in 73% yield by carrying out the reaction in MeCN at 120 °C under the presence K_2CO_3 as the base and 5 equivalents of **4a**. The excess of **4a** was found to play a key role to achieve better product selectivity control (Table 1, entries 11–13).

This protocol was then used when the process was extended to include other indoles **1** and α-amino acid methyl esters **4**. Our preparative results are summarized in Table 2.

Several 2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one derivatives bearing a variety of useful functional groups have been

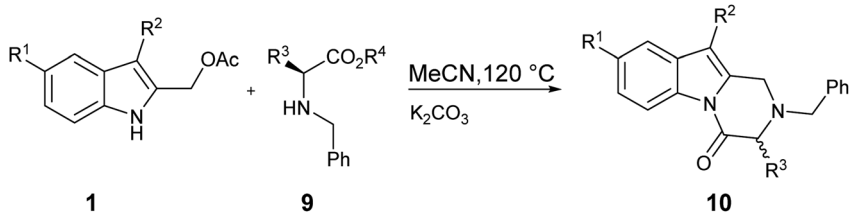
Table 2 Synthesis of 3-substituted-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-ones **5** from **1** and α-amino acid methyl ester **4**[a]



Entry[b]	R^1	R^2	**1**	R^3	**4**	*t* (h)	**5** (%)	**8** (%)
1[c]	H	H	**1a**	$CH_2CH(Me)_2$	**4b**	22	36 **5b**	32 **8b**
2	H	H	**1a**	$CH_2CH(Me)_2$	**4b**	15	59 **5b**	32 **8b**
3[c]	H	H	**1a**	$CH(Me)_2$	**4c**	19	59 **5c**	29 **8c**
4	H	H	**1a**	$CH(Me)_2$	**4c**	19	71 **5c**	13 **8c**
5	Me	H	**1b**	$CH(Me)_2$	**4c**	17	76 **5d**	19 **8d**
6	Me	H	**1b**	CH_2Ph	**4a**	21	44 **5e**	20 **8e**
7	OMe	H	**1c**	CH_2Ph	**4a**	6	67 **5f**	15 **8f**
8	Cl	H	**1d**	CH_2Ph	**4a**	4.5	58 **5g**	6 **8g**[d,e]
9	H	C_6H_5-	**1e**	CH_2Ph	**4a**	6.5	68 **5h**	8 **8h**

[a] Unless otherwise stated, reactions were carried out on a 0.404 mmol scale at 120 °C using 5 equiv. of **4**, 2 equiv. of K_2CO_3 in 3.0 mL of MeCN. [b] Yields are given for isolated products. [c] The reaction was carried out in presence of 2 equiv. of **4**. [d] Yield was calculated from the ^{1}H NMR analyses. [e] **1d** was recovered in 15% of yield.

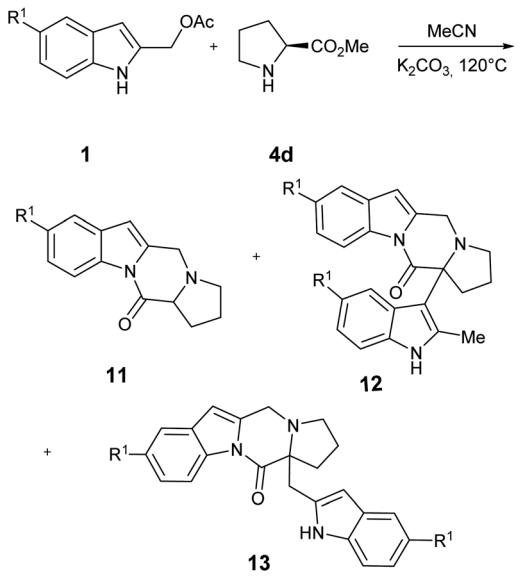
Table 3 Synthesis of *N*-Bn-3-substituted-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-ones **10** from **1** and *N*-Bn-α-amino acid methyl ester **9**[a]



Entry[b]	R^1	R^2	**1**	R^3	R^4	**9**	*t* (h)	**10** (%)
1	H	H	**1a**	CH_2Ph	Me	**9a**	24	84 **10a**
2	H	H	**1a**	$CH(CH_3)_2$	Et	**9b**	48	71 **10b**
3	H	H	**1a**	$CH(CH_3)(C_2H_5)$	Me	**9c**	16	67 **10c**
4	Cl	H	**1d**	$CH(CH_3)(C_2H_5)$	Me	**9c**	17	54 **10d**
5	OMe	H	**1c**	CH_2Ph	Me	**9a**	16	68 **10e**

[a] Unless otherwise stated, reactions were carried out on a 0.290 mmol scale at 120 °C using 1.5 equiv. of **9**, 2 equiv. of K_2CO_3 in 3.0 mL of MeCN. [b] Yields are given for isolated products.

Table 4 Synthesis of 1,2,3,12*a*-tetrahydro-5*H*,12*H*-pyrrolo[1′,2′:4,5]pyrazino[1,2-*a*]indol-12-one **11** from **1** and L-proline methyl ester **4d**[a]



Entry[b]	R^1	1	*t* (h)	**11** (%)	**12** (%)	**13** (%)
1	H	**1a**	20	76 **11a**	8 **12a**	—
2[c]	OMe	**1c**	16	Traces	39 **12c**	**12** **13c**

[a] Unless otherwise stated, reactions were carried out on a 0.404 mmol scale at 120 °C using 2 equiv. of **4d**, 2 equiv. of K_2CO_3 in 3.0 mL of MeCN. [b] Yields are given for isolated products. [c] (1*H*-indol-2-yl) methanol was isolated in 14% yield.

prepared in good yields: in particular, the 5-chloro derivative (Table 2, entry 8) indicates that this protocol is a useful tool for obtaining more complex derivatives through subsequent transition metal-catalyzed cross-coupling reactions.

Indoles bearing electron-releasing and electron-donating groups at the C^5 position show a comparable reactivity for the same α-amino acid **4** (Table 2, entries 6–8) in terms of overall yield and **5**/**8** ratio; this result suggests that the electrophilicity of 5-substituted 2-methide-2*H*-indole intermediates **I**, even modulated by the electronic effects of the substituents, do not affect the reaction outcome in presence of the strong neutral nitrogen nucleophiles **4** and **5**.

Interestingly, the size of the R^3 chain of the α-amino acid **4** seems to play a role in the achievement of the reaction: in fact, while a satisfactory yield was obtained with L-phenylalanine and L-valine methyl ester (Table 1, entry 13 and Table 2, entry 4), a significant lowering in the yield was observed with L-leucine (Table 2, entry 2).

In order to avoid the side formation of **8** using a lower molar excess of nucleophile, we decided to utilize the α-amino acids methyl esters as *N*-benzyl derivatives **9**. The brief investigation done showed that compounds **10** were obtained in good yield (Table 3, entry 1–5) without the isolation of side products. As reported before, the correlation between the steric hindrance of

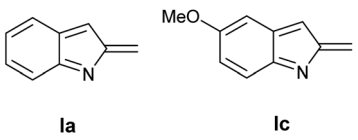


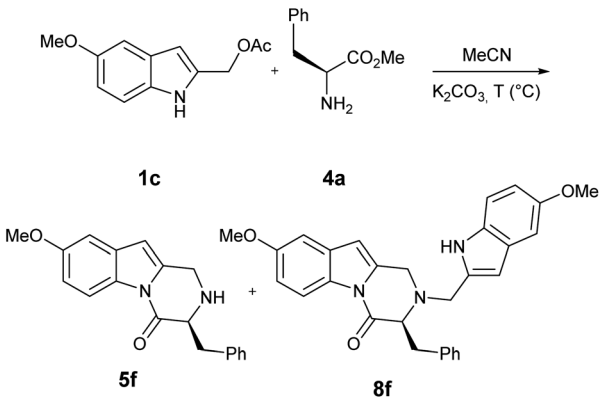
Fig. 2 2-Methide-2*H*-indole I.

the alkyl substituent R^3 in **9** and the yield of the reaction was observed (Table 3, entry 1 *vs.* entry 2–3).

Finally, we briefly investigate the outcome of the reaction using L-proline **4d**, to extend the scope of the process to the construction of the pirrolopirazinoindol-12-one tetracyclic core **11** (Table 4).

Table 4 shows the preliminary results obtained using two different indole precursors **1a** and **1c**. Interestingly, while the reaction between **1a** and L-proline gave the target compound **11a** in large excess over the side products **12a** and **13a** (Table 4, entry 1), using indole derivative **2b** the outcome of the reaction is reversed, being the **12b** and **13b** products the principal, while **1b** was isolated in traces (Table 4, point 2). A tentative explanation of these results could be made by taking into account the electronic effect of 5- substituent on the intermediate **I:** (Fig. 2) to this end, the HF calculations at 631G** level on **Ia** and **Ib** showed a significant difference in the partial positive charge on the methylidene carbon atom (see ESI† for more details).[13] Since the carbanion derived from **11** may be considered highly

Table 5 Effect of temperature in ee[a,b]



Entry[c]	*T* °(C)	*t* (h)	**5f** (%)	e.r.[d]	**8f** (%)
1	120	6	67	68 : 32	15
2	90	6	69	85 : 15	—
3[e]	70	18	31	92 : 8	—
4[f]	70	6	27	95 : 5	—
5[g]	50	24	—		—

[a] Unless otherwise stated, reactions were carried out on a 0.404 mmol scale using 5 equiv. of **4a**, 2 equiv. of K_2CO_3 in 3.0 mL of MeCN. [b] The major enantiomer L is shown. [c] Yields are given for isolated products. [d] e.r was calculated from enantioselective HPLC analysis (see ESI for more details). [e] The starting indole **1c** was recovered in 50% of yield. [f] The starting indole **1c** was recovered in 60% of yield. [g] The starting indole **1c** was recovered almost quantitatively.

delocalized, it is reasonable to believe that the greater electrophilicity of **Ic** prevents an accumulation of the product **11b** but, on the contrary, favors its rapid transformation into **12c** and **13c**.

Because of the crucial role of chiral nitrogen heterocycles in medicinal chemistry, we also analyzed the stereochemical outcome of our synthesis (Table 5).

It has long been noted that amino acids rapidly undergo racemization process when heated in acidic or basic conditions and subsequently our target pyrazoindole could undergo racemization at C3 *via* enolate.[14]

Indeed, when the reaction of **1c** with methyl L-phenylalaninate **4a** was carried out at 120 °C, HPLC analysis showed the formation of **5f** as enantioenriched mixture (68 : 32, Table 5, entry 1), while **8f** was obtained as racemate. The enantiomeric ratio and its dependence on reaction temperature were established by HPLC on Chiralpak IA column of purified pyrazinoindoles. When the reaction was performed at lower temperatures (Table 5, entry 2–4) the loss of enantiomeric purity was limited (up to 95 : 5, Table 5, entry 4).

Experimental

A list of chemicals and instrumentation is provided in the ESI.†

Typical procedure for the preparation of substituted (1*H*-indol-2-yl)methyl acetate 1(a–e)

The (1*H*-indol-2-yl)methyl acetates (**1a–d**) and 3-aryl-2-(1*H*-indol-2-yl)methyl acetates (**1e**) were previously synthesized in our laboratory[10–12] according to the procedures reported in ESI.†

Typical procedure for the preparation of 3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5a

In a 50 mL Carousel Tube Reactor (Radley Discovery Technology) containing a magnetic stirring bar (1*H*-indol-2-yl)methyl acetate **1a** (76.4 mg, 0.404 mmol, 1.0 equiv.) was dissolved at room temperature with 2.0 mL of anhydrous MeCN. Then, methyl L-phenylalaninate **4a** (357.5 mg, 2.020 mmol, 5.0 equiv.), K_2CO_3 (112.0 mg, 0.808 mmol, 2.0 equiv), and 1.0 mL of solvent were added. The mixture was stirred for 18 h at 120 °C. After this time, the reaction mixture was cooled to room temperature, diluted with Et_2O, washed with a saturated $NaHCO_3$ solution and with brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm), eluting with a 80/20 (v/v) *n*-hexane/AcOEt mixture ($R_f = 0.21$) to obtain 81.0 mg (73% yield) of 3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one **5a** and 7.0 mg (8% yield) of 2-((1*H*-indol-2-yl)methyl)-3-benzyl-2,3-dihydropyrazino [1,2-*a*]indol-4(1*H*)-one **8a**.

3-Benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 5a. 73% yield (81.0 mg); brown solid; mp: 120–123 °C; $R_f = 0.21$ (*n*-hexane–EtOAc, 80 : 20); IR (neat): 2989, 2796, 1444, 1272, 1183, 941, 734 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.36 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 7.6$ Hz, 1H), 7.27–7.16 (m, 7H), 6.17 (s, 1H), 4.11 (d, $J = 16$ Hz, 1H), 3.88 (d, $J = 16$ Hz, 1H), 3.79 (dd, $J_1 = 8.7$ Hz, $J_2 = 4.0$ Hz, 1H), 3.44 (dd, $J_1 = 14$ Hz, $J_2 = 4.0$ Hz, 1H), 3.06 (dd, $J_1 = 14.0$ Hz, $J_2 = 8.7$ Hz, 1H), 1.79 (s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.1 (C), 137.5 (C), 136.6 (C), 134.7 (C), 129.5 (CH), 128.8 (CH), 127.0 (CH), 124.5 (CH), 124.2 (CH), 120.2 (CH), 116.3 (CH), 103.1 (CH), 61.3 (CH), 41.9 (CH_2), 36.3 (CH_2). HRMS: m/z $[M + H]^+$ calcd for $C_{15}H_{17}NO_2$: 277.1335; found: 277.1336.

2-((1*H*-Indol-2-yl)methyl)-3-benzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 8a. 8% yield (7.0 mg); yellow solid; mp: 107–110 °C; $R_f = 0.22$ (*n*-hexane–EtOAc, 85 : 15); IR (neat): 3401, 2986, 2808, 1692, 1356, 1188, 691 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.40 (d, $J = 7.9$ Hz, 1H), 7.48 (d, $J = 6.8$ Hz, 1H), 7.41–7.18 (m, 10H), 7.06–7.02 (m, 1H), 7.00–6.94 (m, 2H), 6.36 (s, 1H), 6.11 (s, 1H), 4.43 (dd, $J_1 = 16.7$, $J_2 = 1.8$ Hz, 1H), 3.89–3.82 (m, 2H), 3.74–3.69 (m, 2H), 3.25 (dd, $J_1 = 14.1$, $J_2 = 4.3$ Hz, 1H), 3.09 (dd, $J_1 = 14.2$, $J_2 = 11.5$ Hz, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 168.8 (C), 138.3 (C), 136.0 (C), 134.9 (C), 134.6 (C), 133.9 (C), 129.7 (C), 129.5 (CH), 128.8 (CH), 128.3 (C), 127.1 (CH), 124.9 (CH), 124.6 (CH), 121.7 (CH), 120.5 (CH), 120.2 (CH), 119.7 (CH), 116.5 (CH), 111.0 (CH), 105.8 (CH), 101.5 (CH), 64.6 (CH), 52.0 (CH_2), 43.5 (CH_2), 35.6 (CH_2). HRMS: m/z $[M + H]^+$ calcd for $C_{27}H_{24}N_3O$: 406.1914; found: 406.1915.

Typical procedure for the preparation of 2,3-dibenzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 10a

In a 50 mL Carousel Tube Reactor (Radley Discovery Technology) containing a magnetic stirring bar (1*H*-indol-2-yl)methyl acetate (54.9 mg, 0.290 mmol, 1.0 equiv.) was dissolved at room temperature with 2.0 mL of anhydrous MeCN. Then, methyl benzyl L-phenylalaninate (369.8 mg, 1.45 mmol, 5.0 equiv.), K_2CO_3 (80.0 mg, 0.58 mmol, 2.0 equiv.), and 1.0 mL of solvent were added. The mixture was stirred for 24 h at 120 °C. After this time, the reaction mixture was cooled to room temperature, diluted with Et_2O, washed with a saturated $NaHCO_3$ solution, and with brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm), eluting with a 96/4 (v/v) *n*-hexane/AcOEt mixture ($R_f = 0.21$) to obtain 89.2 mg (84% yield) of 2,3-dibenzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one.

2,3-Dibenzyl-2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-one 10a. 84% yield (89.3 mg); pale pink solid; mp: 115–116 °C; $R_f = 0.21$ (*n*-hexane–EtOAc, 96 : 4); IR (neat):3024, 1782, 1450, 1373, 695 cm^{-1}; ^1H NMR (400.13 MHz) ($CDCl_3$): δ 8.54 (d, $J = 7.9$ Hz, 1H), 7.58 (d, 1H), 7.43–7.31 (m, 7H), 7.29–7.22 (m, 3H), 7.05–7.03 (m, 2H), 6.41 (s, 1H), 4.39 (dd, $J_1 = 16.9$, $J_2 = 1.7$ Hz, 1H), 3.93 (d, $J = 4.4$ Hz, 1H), 3.90 (d, 1H), 3.82 (d, $J = 13.3$ Hz, 1H), 3.66 (d, $J = 13.3$ Hz, 1H), 3.35 (dd, $J_1 = 14.4$, $J_2 = 4.9$ Hz, 1H), 3.25 (dd, $J_1 = 14.4$, $J_2 = 10.1$ Hz, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 169.4 (C), 138.2 (C), 137.6 (C), 134.9 (C), 134.6 (C), 129.7 (C), 129.4 (CH), 128.8 (CH), 128.4 overlapping (CH), 127.5 (CH), 126.7 (CH), 124.6 (CH), 124.3 (CH), 120.3 (CH), 116.5 (CH), 105.4 (CH), 66.4 (CH), 58.1 (CH_2), 43.1 (-CH_2), 35.5 (CH_2). HRMS: m/z $[M + H]^+$ calcd for $C_{25}H_{23}N_2O$: 367.1805; found: 367.1804.

Conclusions

To sum up, this paper describes a general protocol for the synthesis of 2,3-dihydropyrazino[1,2-*a*]indol-4(1*H*)-ones from

readily available indole-2-ylmethyl acetates. The reaction tolerates a variety of useful neutral, electron-rich, and electron-poor substituents and proceeds through *in situ* generation under basic conditions of highly unstable and reactive 2-alkylideneindolenines followed by Michael-type additions of α-amino acids methyl ester/intramolecular cyclization. The influence of the reaction conditions and the features of substrates on the stereochemical outcome of the procedure with the use of chiral α-amino esters has been explored.

Author contributions

Conceptualization: G. F.; data curation: A. A. and A. S.; funding acquisition: G. F.; investigation: A. C., M. D. A., S. D., F. I., A. I., and R. Z.; methodology: A. G. and A. S.; project administration: G. F.; supervision: A. G.; writing—original draft: A. G.; writing—review and editing: A. I., A. A., and A. S. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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