Facile Synthesis of 6-Aryl-5*H*-8-oxa-4*b*, 7-diaza-benzo[*a*]azulen-9-one Derivatives, New Tricyclic Heterocycles

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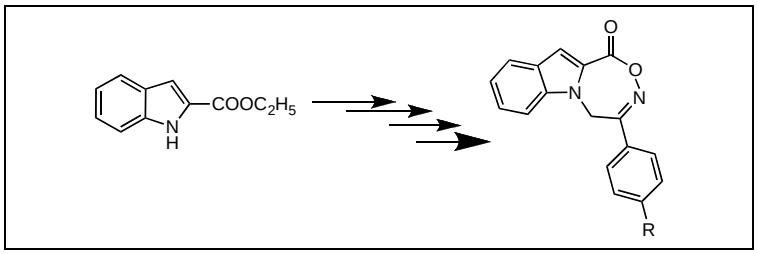

8-Oxa-*4b*,7-diaza-benzo[*a*]azulene-9-one system, a new tricyclic heterocyclic framework is designed through a simple and convenient synthetic sequence. Its 6-aryl derivatives are synthesized starting from ethyl indole-2-carboxylate. Reaction of differently substituted phenacyl bromides with ethyl indole-2-carboxylate, treatment of the resultant N-substituted indole-2-carboxylates with hydroxylamine hydrochloride to provide corresponding oximes, subsequent ester hydrolysis followed by dehydrative cyclisation furnished the desired compounds **5 a-g**.

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INTRODUCTION

The substituted indole nucleus is found in several natural products [1-3]. Being very important in medicinal chemistry, its synthesis continues to attract significant interest [4-8]. A variety of well-established classical methods for the synthesis and functionalization of indoles are known in the literature [9]. There are very few reports on the reactions of indole-2-carboxylates substituted on nitrogen with phenacyl groups [10].

As part of our ongoing research work on N-substituted indole-2-carboxylates, we became interested in the design and synthesis of new fused tricyclic heterocyclic compounds **5a-g**. Ethyl indole-2-carboxylate (**1**), which can be readily accessed from commercially available indole-2-carboxylic acid, was chosen as the starting material.

RESULTS AND DISCUSSION

Ethyl indole-2-carboxylate **1** was reacted with 4-methyl phenacyl bromide in the presence of potassium carbonate in refluxing acetone to give the N-phenacyl derivative **2a**, which on condensation with hydroxylamine hydrochloride in ethanol in the presence of sodium acetate at reflux temperature gave the corresponding oxime **3a**.

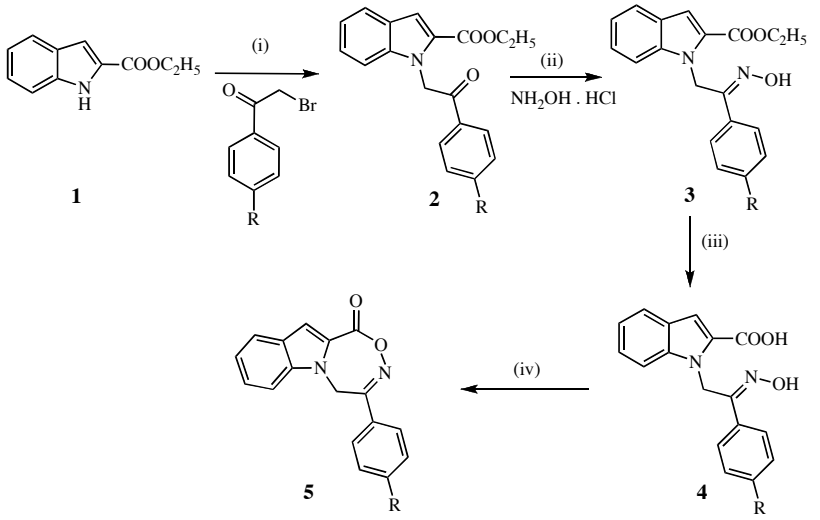
Hydrolysis of ester function in **3a** with aqueous NaOH in ethanol smoothly yielded the N-substituted indole carboxylic acid derivative **4a** which readily underwent acetic anhydride mediated cyclisation at room temperature to provide 6-(*p*-methylphenyl)-5*H*-8-oxa-*4b*,7-diaza-benzo[*a*]azulene-9-one (**5a**). 8-Oxa-*4b*,7-diaza-benzo[*a*]-azulene-9-one is a new fused tricyclic heterocyclic system hitherto unreported.

To verify the generality of this synthetic sequence, we have extended this synthetic sequence to six other *p*-substituted phenacyl bromides and in all the corresponding 6-aryl-5*H*-8-oxa-4*b*,7-diaza-benzo[*a*]-azulen-9-one derivatives, **5b-g** were obtained as final products (Scheme). All the compounds, **2a-g, 3a-g, 4a-g** and **5a-g** are fully characterized based on their IR, ^{1}H- NMR and Mass spectral data (Table-2).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, on a Varian Gemini 200 MHz FT NMR spectrometer. The chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin–Elmer 1650 FTIR spectrophotometer. The mass spectrum (70 eV) was recorded on a HP-5989a LC–MS spectrometer and C, H, N analysis was done

Scheme 1



2,3,4,5	a	b	c	d	e	f	g
R	p-CH_3	p-OCH_3	p-H	p-SCH_3	p-C_2H_5	p-Isobutyl	p-Cl

Reagents and conditions: (i) Acetone, K_2CO_3, reflux (ii) Ethanol, CH_3COONa, reflux (iii) NaOH, ethanol, RT (iv) Acetic anhydride, RT.

Table-1

Physical and analytical data of **2a-g, 3a-g, 4a-g, 5a-g**

Compound	R	Yield (%)	MP (°C)	Molecular formula	Analyses % Calcd/Found		
					C	H	N
2a	p-CH_3	78	134-136	$C_{20}H_{19}NO_3$	74.75/74.61	5.96/5.87	4.36/4.24
2b	p-OCH_3	74	128-130	$C_{20}H_{19}NO_4$	71.20/71.12	5.68/5.57	4.15/4.14
2c	H	75	120-122	$C_{19}H_{17}NO_3$	74.25/74.10	5.58/5.49	4.56/4.47
2d	p-SCH_3	79	126-128	$C_{20}H_{19}NO_3S$	67.97/67.83	5.42/5.36	3.96/3.87
2e	p-C_2H_5	70	117-119	$C_{21}H_{21}NO_3$	75.20/75.11	6.31/6.24	4.18/4.15
2f	p-Isobutyl	69	125-126	$C_{23}H_{25}NO_3$	76.01/75.89	6.93/6.82	3.85/3.76
2g	p-Cl	66	143-145	$C_{19}H_{16}ClNO_3$	66.77/66.62	4.72/4.65	4.10/3.94
3a	p-CH_3	79	122-124	$C_{20}H_{20}N_2O_3$	71.41/71.32	5.99/5.88	8.33/8.25
3b	p-OCH_3	83	116-118	$C_{20}H_{20}N_2O_4$	68.17/68.00	5.72/5.64	7.95/7.86
3c	H	86	110-112	$C_{19}H_{18}N_2O_3$	70.79/70.86	5.63/5.54	8.69/8.58
3d	p-SCH_3	81	126-127	$C_{20}H_{20}N_2O_3S$	65.20/65.15	5.47/5.35	7.60/7.52
3e	p-C_2H_5	86	118-119	$C_{21}H_{22}N_2O_3$	71.98/71.92	6.33/6.24	7.99/7.88
3f	p-Isobutyl	80	105-106	$C_{23}H_{26}N_2O_3$	72.99/72.87	6.92/6.84	7.40/7.33
3g	p-Cl	75	128-130	$C_{19}H_{17}ClN_2O_3$	63.96/63.87	4.80/4.74	7.85/7.76
4a	p-CH_3	89	228-230	$C_{18}H_{16}N_2O_3$	70.12/70.14	5.23/5.11	9.09/8.97
4b	p-OCH_3	86	219-220	$C_{18}H_{16}N_2O_4$	66.66/66.57	4.97/4.86	8.64/8.56
4c	H	83	225-226	$C_{17}H_{14}N_2O_3$	69.38/69.24	4.79/4.87	9.52/9.45
4d	p-SCH_3	81	210-212	$C_{18}H_{16}N_2O_3S$	63.51/63.44	4.74/4.66	8.23/8.15
4e	p-C_2H_5	80	220-222	$C_{19}H_{18}N_2O_3$	70.79/70.67	5.63/5.55	8.69/8.61
4f	p-Isobutyl	81	209-210	$C_{21}H_{22}N_2O_3$	71.98/71.87	6.33/6.24	7.99/7.88
4g	p-Cl	77	234-236	$C_{17}H_{13}ClN_2O_3$	62.11/62.00	3.99/3.87	8.52/8.45
5a	p-CH_3	61	210-212	$C_{18}H_{14}N_2O_2$	74.47/74.38	4.86/4.77	9.65/9.56
5b	p-OCH_3	67	213-214	$C_{18}H_{14}N_2O_3$	70.58/70.47	4.61/4.54	9.15/9.04
5c	H	66	206-207	$C_{17}H_{12}N_2O_2$	73.90/73.88	4.38/4.31	10.14/10.12
5d	p-SCH_3	62	220-222	$C_{18}H_{14}N_2O_2S$	67.06/66.93	4.38/4.29	8.69/8.58
5e	p-C_2H_5	69	201-202	$C_{19}H_{16}N_2O_2$	74.98/74.86	5.30/5.21	9.20/9.11
5f	p-Isobutyl	62	192-194	$C_{21}H_{20}N_2O_2$	75.88/75.79	6.06/5.97	8.43/8.36
5g	p-Cl	57	210-220	$C_{17}H_{11}ClN_2O_2$	65.71/65.59	3.57/3.48	9.02/8.95

Table-2

IR, Mass and ^{1}H NMR spectral analysis for compounds **2a-g 3a-g, 4a-g, 5a-g**

Compound	IR (KBr) (ν/Cm^{-1})	Mass (m/z)	^{1}H NMR (Solvent/δ values in ppm)
2a	Aromatic(C=O) 1608 Ester (C=O) 1697	322(M^{+1})	(DMSO-d_6): 1.2 (t, 3H), 2.4 (s, 3H), 4.3 (q, 2H), 6.1(s, 2H), 7.14 (t, 1H), 7.34 (m, 4H), 7.36 (dd, 2H), 8.0 (d, 2H)
2b	Aromatic (C=O) 1606 Ester (C=O) 1695	338(M^{+1})	(DMSO-d_6): 1.3 (t, 3H), 3.8 (s, 3H), 4.2 (q, 2H), 5.9(s, 2H), 7.1 (t, 1H), 7.3 (m, 4H), 7.4 (dd, 2H), 8.1 (d, 2H)
2c	Aromatic (C=O) 1608 Ester (C=O) 1695	308(M^{+1})	(DMSO-d_6): 1.25 (t, 3H), 4.3 (q, 2H), 6.0(s, 2H), 7.14 -8.0 (d, 2H)
2d	Aromatic (C=O) 1604 Ester (C=O) 1699	354(M^{+1})	(DMSO-d_6): 1.2 (t, 3H), 3.1 (s, 3H), 4.3 (q, 2H), 5.8(s, 2H), 7.2 (t, 1H), 7.4 (m, 4H), 7.5 (dd, 2H), 8.0 (d, 2H)
2e	Aromatic(C=O) 1604 Ester (C=O) 1698	336(M^{+1})	(DMSO-d_6): 1.3 (t, 3H), 1.2 (t, 3H), 2.4 (q, 2H), 4.4 (q,2H), 6.0 (s, 2H), 7.2 (t, 1H), 7.3 (m, 4H), 7.4 (dd, 2H), 8.1 (d, 2H)
2f	Aromatic(C=O) 1606 Ester (C=O) 1697	364(M^{+1})	(DMSO-d_6): 1.1 (d, 6H), 1.4 (t, 3H), 2.3 (m, 1H), 2.6 (d, 2H), 4.3 (q, 2H), 6.2(s, 2H), 7.2 (t, 1H), 7.4 (m, 4H), 7.6 (dd, 2H), 8.1 (d, 2H)
2g	Aromatic (C=O) 1603 Ester (C=O) 1692	342(M^{+1})	(DMSO-d_6): 1.25 (t, 3H), 4.5 (q, 2H), 6.2(s, 2H), 7.2 -8.1 (m, 8H)
3a	3244 (OH) 1700 (C=O) 1609 (C=N)	337(M^{+1})	($CDCl_3$): 1.2 (m, 3H), 2.2 (s, 3H), 4.7 (q, 2H), 5.65 (s, 1H), 6.0 (s, 2H), 6.9 (d, 1H), 7.0-7.8 (m, 8H)
3b	3238 (OH) 1704 (C=O) 1612 (C=N)	353(M^{+1})	($CDCl_3$): 1.3 (d, 3H), 3.6 (s, 3H), 4.4 (q, 2H), 5.5 (s, 1H), 6.9 (s, 2H), 7.0 (d, 1H), 7.3-8.1 (m, 8H)
3c	3230 (OH) 1710 (C=O) 1610 (C=N)	323(M^{+1})	($CDCl_3$): 1.3 (m, 3H), 4.7 (q, 2H), 5.1 (s, 1H), 6.1 (s, 2H), 6.9 (d, 1H), 7.2-7.9 (m, 9H)
3d	3240 (OH) 1708 (C=O) 1612 (C=N)	379(M^{+1})	($CDCl_3$): 1.3 (d, 3H), 3.4 (s, 3H), 4.2 (q, 2H), 5.6 (s, 1H), 7.1 (s, 2H), 7.2 (d, 1H), 7.4-8.2 (m, 8H)
3e	3238 (OH) 1704 (C=O) 1606 (C=N)	351(M^{+1})	($CDCl_3$): 1.2 (m, 3H), 1.3 (m, 3H), 2.5 (q, 2H), 4.4 (q, 2H), 5.1 (s, 1H), 6.0 (s, 2H), 7.0 (d, 2H), 7.2-7.8 (m, 8H)
3f	3233 (OH) 1704 (C=O) 1604 (C=N)	389(M^{+1})	($CDCl_3$): 1.0 (d, 6H), 2.2 (m, 1H), 2.5 (d, 2H), 4.2 (q, 2H), 4.9 (s, 1H), 6.1 (s, 2H), 7.1 (d, 2H), 7.2-7.9 (m, 8H)
3g	3236 (OH) 1704 (C=O) 1607 (C=N)	351 (M^{+1})	($CDCl_3$): 1.25 (d, 3H), 4.2 (q, 2H), 5.0 (s, 1H), 6.1 (s, 2H), 7.0 (d, 2H), 7.0-7.8 (m, 8H)
4a	3526 (Acid OH) 3366(oxime-OH) 1675 (C=O) 1638 (C=N)	307(M-1)	(CDCl3+DMSO-d6): 2.2 (s, 3H), 5.7 (s, 1H), 6.1 (s, 2H), 6.8 (d, 1H), 6.9-7.6 (m, 8H)
4b	3520 (Acid OH) 3361 (oxime-OH) 1672 (C=O) 1634 (C=N)	323(M-1)	(CDCl3+DMSO-d6): 3.7 (s, 3H), 5.2 (s, 1H), 6.0 (s, 2H), 7.0 (d, 1H), 7.2-7.9 (m, 8H)
4c	3530 (Acid OH) 3350 (oxime-OH) 1669 (C=O) 1640 (C=N)	293(M-1)	(CDCl3+DMSO-d6): 4.8 (s, 1H), 5.9 (s, 2H), 6.7 (d, 1H), 6.9-7.7(m, 9H)

Table 2 (continued)

Compound	IR (KBr) (ν/Cm^{-1})	Mass (m/z)	^{1}H NMR (Solvent/δ values in ppm)
4d	3521 (Acid OH) 3360 (oxime-OH) 1673 (C=O) 1632 (C=N)	349(M^{-1})	($CDCl_3$+DMSO-d_6): 3.4 (s, 3H), 4.9 (s, 1H), 5.9 (s, 2H), 6.8 (d, 1H), 7.0-7.8 (m, 8H)
4e	3520 (Acid OH) 3361 (oxime-OH) 1672 (C=O) 1634 (C=N)	321(M^{-1})	($CDCl_3$+DMSO-d_6): 1.2 (t, 3H), 2.5 (q, 2H), 4.5 (s, 1H), 6.0 (s, 2H), 6.7 (d, 1H), 7.0-7.9 (m, 8H)
4f	3529 (Acid OH) 3360 (oxime-OH) 1672(C=O) 1638(C=N)	359(M^{-1})	($CDCl_3$+DMSO-d_6): 1.1 (d, 6H), 2.2 (m, 1H), 2.45 (d, 2H) 4.6 (s, 1H), 5.9 (s, 2H), 6.7 (d, 1H), 7.0-7.9 (m, 8H)
4g	3519 (Acid OH) 3362(oxime-OH) 1671(C=O) 1634(C=N)	321 (M^{-1})	($CDCl_3$+DMSO-d_6): 4.2 (s, 1H), 5.8 (s, 2H), 7.1 (d, 1H), 7.2-8.0 (m, 8H)
5a	1716 (C=O) 1678(C=N)	289(M^{+1})	($CDCl_3$): 2.4 (s, 3H), 5.4 (s, 1H of N-CH_2), 6.4 (s, 1H of N-CH_2), 7.1-7.8 (m, 8H), 8.3 (d,1H)
5b	1717 (C=O) 1675 (C=N)	307(M^{+1})	($CDCl_3$): 3.8 (s, 3H), 5.45 (s, 1H of N-CH_2), 6.6 (s, 1H of N-CH_2), 6.9-7.7 (m, 8H), 8.3 (d, 1H)
5c	1712 (C=O) 1672 (C=N)	275(M^{+1})	($CDCl_3$): 5.5 (s, 1H of N-CH_2), 6.35 (s, 1H of N-CH_2), 7.2-7.9 (m, 8H), 8.3 (d, 1H)
5d	1714 (C=O) 1677(C=N)	323(M^{+1})	($CDCl_3$): 2.9 (s, 3H), 5.7 (s, 1H of N-CH_2), 6.6 (s, 1H of N-CH_2), 7.2-7.9 (m, 8H), 8.25 (d, 1H)
5e	1713 (C=O) 1675 (C=N)	305(M^{+1})	($CDCl_3$): 1.4 (t, 3H), 2.5 (q, 2H), 5.8 (s, 1H of N-CH_2), 6.6 (s, 1H of N-CH_2), 7.0-7.7 (m,8H), 8.35 (d,1H)
5f	1716(C=O) 1678(C=N)	333(M^{+1})	($CDCl_3$): 1.2 (d, 6H), 2.2 (m, 1H), 2.5 (d, 2H), 5.4 (s, 1H of N-CH_2), 6.6 (s, 1H of N-CH_2), 7.2-7.9 (m, 8H), 8.3 (d, 1H)
5g	1716(C=O) 1676(C=N)	311(M^{+1})	($CDCl_3$): 5.5 (s, 1H of N-CH_2), 6.6 (s, 1H of N-CH_2), 7.3-7.9 (m, 8H), 8.35 (d, 1H)

using Perkin-Elmer 2100. The melting points were determined by using the capillary method on a POLMON (model MP-96) melting point apparatus. The solvents and reagents were used without any purification. The reactions were routinely monitored by thin layer chromatography (TLC) on silica gel plates.

General procedure for the preparation of ethyl 1-(2-oxo-2-aryl-ethyl)-1*H*-indole-2-carboxylates 2a-g. To a solution of ethyl indole-2-carboxylate (**1**, 50 g, 0.264 mol) in acetone (350 mL) was added phenacyl bromide (0.264 mol), potassium carbonate (0.528 mol) and catalytic amount of potassium bromide and was refluxed for 4-5 hours. Acetone was stripped off and the reaction mixture was then quenched in water and filtered to get the crude product **2a-g** which was recrystallised from acetone to give the pure product.

General procedure for the preparation of ethyl 1-(2-Hydroxyimino-2-aryl-ethyl)-1*H*-indole-2-carboxylates 3a-g. A mixture of ethyl 1-(2-oxo-2-aryl-ethyl)-1*H*-indole-2-carboxylate (**2**, 0.062 mol), hydroxylamine hydrochloride (0.187 mol) and sodium acetate (0.187 mol) was refluxed in ethanol for 30 min. The reaction mixture was quenched with ice water, crude product **3a-g** was filtered and recrystallised from ethanol.

General procedure for the preparation of 1-(2-hydroxyimino-2-aryl-ethyl)-1*H*-indole-2-carboxylic acids 4a-g. To a solution of ethyl 1-(2-hydroxyimino-2-aryl-ethyl)-1*H*-indole-2-carboxylate **3** (0.074 mol) in 50 mL of ethanol was added 300 mL of 1N sodium hydroxide solution and the mixture was stirred at room temperature for 12 hours. After completion of the reaction, the reaction mixture was acidified with acetic acid to precipitate the compound **4**. The crude compound was filtered and washed with water to get the compound **4a-g.**

General procedure for the preparation of 6-aryl-5*H*-8-oxa-4b,7-diaza-benzo[*a*]azulen-9-one 5a-g. A solution of compound **4** (0.32 mol) in acetic anhydride (40 mL) was stirred for 6 hours at ambient temperature. The reaction mixture was quenched in ice water and extracted with methylene chloride. The solvent was evaporated under reduced pressure and the crude product **5** was isolated in methanol. The crude product was recrystallised from acetone to get the pure compound **5a-g**.

Conclusion. In conclusion we have described a simple and efficient synthetic route for 8-oxa-*4b*,7-diaza-benzo[*a*]azulene-9-one system, a new tricyclic heterocyclic framework and its 6-aryl derivatives. Further investigations are under progress to enlarge the scope of these heterocycles.

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