Regioselective Three-component Synthesis of Novel Indeno[1,2-*b*]-pyrazolo[4,3-*e*]pyridines-Fused Derivatives of 4-Azafluorenone Alkaloid

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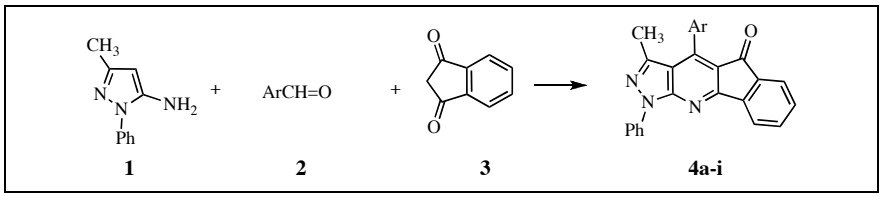
Received April 24, 2007



New fused indeno[1,2-*b*]pyridine derivatives have been prepared in a multicomponent reaction from benzaldehydes, indanedione and the appropriate aminoheteroaryl compound. The simple methodology permitted the syntheses of a series of indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridines **4** from 5-aminopyrazol **1** and modulated by the corresponding benzaldehyde **2**.

J. Heterocyclic Chem., **45**, 155 (2008).

INTRODUCTION

Multi-component reactions, an important class of organic tandem reactions, are one-pot processes with at least three components to form a single product, which incorporates most or even all of atoms of the starting materials [1]. During the past ten years, the huge potential of such multi-component reactions has been applied to develop large libraries of organic compounds by combinatorial chemistry procedures in a facile and benign fashion, because of both high efficiency and convenience in comparison with multistage procedures. Hence, most of the scientific efforts have been focus on the development of multicomponent procedures to prepare diverse heterocyclic compound libraries [1b].

On the other hand, six-membered nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties [2]. The 4-azafluorenone alkaloids (indeno[1,2-*b*]pyridines) comprise a small but biologically intriguing group of alkaloids. The simplest member of this family, Onychine (Figure 1), was first isolated from the Brazilian *Annonaceae* species (*onychopetalum amazonicum*, *Guatteria dielsiana*) in 1976 and has shown to have anticandidal activity [3].

Recently, onychine derivatives were found to exhibit adenosine A2, a receptor binding and phosphodiesterase inhibiting activities for the treatment of neurodegenerative disorders and inflammation related diseases [4]; and also used as calcium antagonists [5] or herbicides [6]. As a result, the development of simple and efficient procedures to the synthesis of analogues of these alkaloids, containing indenopyridine scaffold, has attracted considerable attention [7].

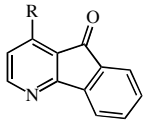


Figure 1. Onychine

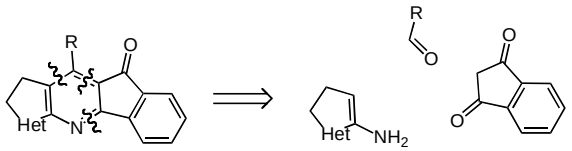
Several approaches have been developed for the synthesis of the indeno[1,2-*b*]pyridin-5-ones: oxidative thermal rearrangement of 2-indanone oxime O-ally1 ethers [7]; direct cyclization of 2-aryl-3-methylpyridines to give 5*H*-indeno[1,2-*b*]pyridines followed by oxidation [7b]; cyclization of 2-aryl-3-nicotinic acids by the use of polyphosphoric acid [7b,8], or by extrusion of organophosphorus compounds [9]. However, even these methods are still not satisfactory in view of using toxic catalyst, narrow application scope of substrates, harsh reaction conditions, scarce generality and operational complexity due to the occurrence of several competitive side reactions.

RESULTS AND DISCUSSION

Having in mind all the benefits of the multicomponent cyclocondensation procedures [10] to build heterocyclic

scaffolds [11], we have planned a facile three-component reaction for the construction of fused indeno[1,2-*b*]-pyridines heterocycles using an aminoheteroaryl, a carbonyl derivative and indanedione **3** (Scheme 1).

Scheme 1



The use of 5-aminopyrazol **1**, benzaldehydes **2** led as predicted to a series of novel indeno[1,2-*b*]pyrazolo-[4,3-*e*]pyridines **4**. Accordingly, a mixture of equimolar amounts of starting compounds such as amine, aldehydes and indandione in DMF was refluxed during 6-8 hours to render compounds **4** in acceptable yields (Scheme 2, Table 1).

Scheme 2

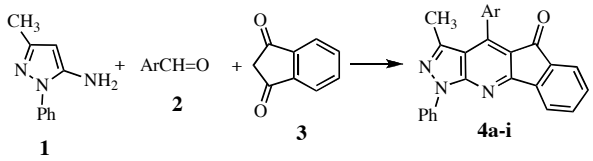


Table 1

Synthesis of indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridines

Entry	Ar	Reaction Time (h)	Yields (%)
4a	C_6H_5	6	58
4b	4-$CH_3C_6H_4$	6	52
4c	4-$CH_3OC_6H_4$	6	47
4d	4-FC_6H_4	7	54
4e	4-$CF_3C_6H_4$	8	51
4f	4-ClC_6H_4	5	49
4g	4-BrC_6H_4	7.5	69
4h	2-FC_6H_4	8	58
4i	3,4-$OCH_2OC_6H_3$	8	68

The structures of all isolated compounds were assigned by 1D and 2D NMR and mass spectrometries (Tables 2 and 3). Based on 1D and 2D NMR experiments such HSQC, HMBC and NOESY techniques, it was possible to assign all protons and carbon atoms of new products.

The NMR data are consistent with structures **4** (Table 2 and 3). For example compound **4c** exhibits a ^{1}H NMR spectrum with two doublets at 7.97 and 8.29 ppm corresponding to CH_3O-phenyl group, multiplets corresponding to N-phenyl group and indene fragment and a singlet at 2.11 ppm corresponding to CH_3-group at position 3 (see Table 2).

Table 2

^{1}H-NMR Chemical Shifts (δ) for compunds **4a-i**.

Comp.	CH_3	Phenyl	Indene	Aryl C
4a	1.98	8.28, 7.61,7.38	7.60, 7.54, 7.70, 7.96	7.55, 7.56, 7.51
4b	2.09	8.31, 7.53, 7.33	7.60, 7.42, 7.56, 7.96	7.34, 7.54
4c	2.11	8.30, 7.53, 7.34	7.60, 7.43, 7.56, 7.94	7.05, 7.39
4d	2.08	8.30, 7.54, 7.36	7.60, 7.43, 7.59, 7.97	7.22, 7.45
4e	2.03	8.29, 7.55, 7.36	7.60, 7.43, 7.59, 7.97	7.58, 7.80
4f	2.02	8.27, 7.60-7.52, 7.38	760-7.52, 7.94	7.70, 760-7.52
4g	2.02	8.27, 7.61-7.50, 7.39	7.74-7.68, 7.48-7.45, 7.94	7.74-7.68
4h	2.14	8.31, 7.55, 7.35	7.63, 7.43, 7.59, 7.99	7.26,7.40, 7.31
4i	2.15	8.31, 7.54, 7.34	7.60, 7.43, 7.58, 7.96	6.98, 6.95, 6.90

For **4b** CH_3 2.16 ppm; **4c** CH_3O 3.92 ppm; **4i** –OCH_2O- 6.09 ppm

In the ^{13}C (DEPT) all signals belonging to tertiary, secondary and primary carbon atoms could be determined for **4a-i** compounds (Table 3).

We assume that the synthesis of **4** proceed by a *Michael* type addition of the most nucleophilic ring carbon atom in aminopyrazole **1** to the activated double bond of intermediate **5** (formed by Knovenagel condensation between benzaldehyde **2** and indandione **3**) and posterior cyclization of **6** with elimination of a hydrogen and water molecules yield the indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridines **4** (Scheme 3). Similar pathway was described in the multicomponent reaction of indanedione with aldehydes, acetophenones and ammonium acetate [12].

A related behavior was observed when we studied the similar three-component reaction between 6-aminopyrimidine **8**, benzaldehydes **2** and indandione **3**, which when carried out lead to the formation of the corresponding indeno[1,2:2,3]pyrido[2,3-*d*]pyrimidines **9** (Scheme 4). In this reaction, the stable hydrated intermediate **10** was isolated which suffered the aromatization by elimination of a hydrogen and water molecules to render the final product **9** [13].

Regarding to the mass spectra, all products **4** exhibit similar pattern of fragmentation, showing the molecular ion peak along with a typical loss of the substituents of each aryl group.

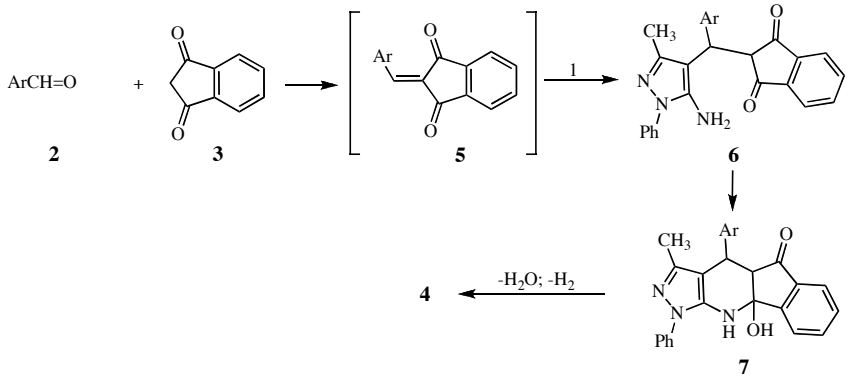
Table 3

^{13}C-NMR Chemical Shifts (δ) for compunds **4a-i**.

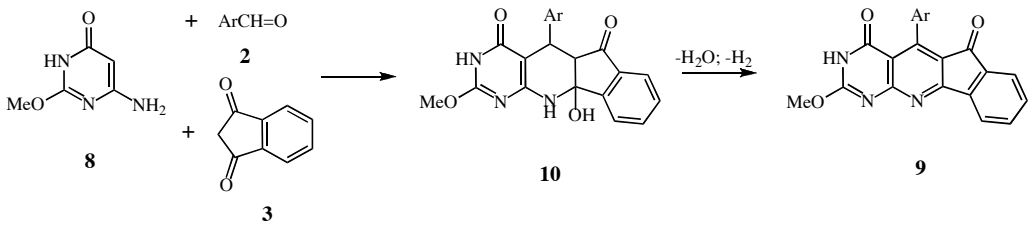
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**
CH_3	13.4	15.3	15.2	15.0	14.9	13.6	13.6	15.3	15.3
C3	144.8	146.3	146.1	145.7	145.5	144.6	144.6	145.7	145.8
C3a	114.7	115.7	115.8	115.6	115.1	114.4	114.3	115.6	115.7
C4	141.2	142.4	142.4	142.4	142.4	141.1	141.1	142.5	142.4
C4a	119.2	120.1	120.1	120.1	119.9	119.2	119.1	120.7	120.2
C5	188.0	189.9	190.0	189.9	189.7	188.0	188.0	189.7	189.9
C5a	136.3	137.4	137.4	137.3	137.2	136.3	136.3	137.4	137.4
C9a	163.8	165.1	165.2	165.1	165.0	163.8	163.8	164.9	165.1
C9b	151.9	152.8	152.8	152.8	152.8	151.9	151.9	152.9	152.8
C9c	144.9	146.0	145.9	144.8	143.7	143.4	143.4	134.6	145.6
Phenyl									
C_i	138.1	139.0	139.1	138.9	138.9	138.1	138.1	139.0	139.0
C_o	120.6	121.6	121.5	121.6	121.6	120.7	120.7	121.6	121.6
C_m	128.4	128.7	129.0	129.1	129.1	128.4	128.4	129.1	129.0
C_p	125.7	126.3	126.3	126.5	126.6	125.7	125.7	126.4	126.4
Aryl									
C_i	122.4	123.4	123.4	123.5	123.6	122.5	122.5	123.6	123.4
C_o	131.1	131.4	131.4	131.6	131.7	131.2	131.3	131.6	131.4
C_m	134.4	134.6	134.6	134.8	135.0	134.5	134.5	134.8	134.7
C_p	120.5	121.4	121.4	121.5	121.5	120.5	120.6	121.5	121.4
Aryl C									
C1	132.0	129.7	124.6	162.1	122.7	130.8	122.0	158.3	126.1
C2	127.0	129.3	113.4	115.3	129.2	127.2	130.1	160.7	122.8
C3	128.2	129.0	130.5	128.6	125.1	130.1	130.3	131.3	148.5
C4	128.1	139.1	160.5	164.6	136.6	133.5	130.2	123.9	147.4

For **4b** CH_3 21.6 ppm; **4c** CH_3O 55.3 ppm; **4e** CF_3 125.4; **4i** $-OCH_2O-$ 65.9 ppm

Scheme 3



Scheme 4



Finally, the isolation of single crystals of compound **4d** permitted the X-ray diffraction analysis that was used to corroborate unambiguously the postulated structures [14].

In summary, we have developed a multi-component condensation to obtain fused indeno[1,2-*b*]pyridine heterocycles, which was applied to prepare a series of poly-substituted indeno[1,2-*b*]pyrazolo[4,3-*e*]pyridines from 5-aminopyrazole, 1,3-indanedione and aromatic aldehydes in a easy fashion. The application of a similar procedure with 6-aminopyrimidine rendered the related indeno[1,2:2,3]pyrido[2,3-*d*]pyrimidine. In light of its operational simplicity, simple purification procedure, good yields, and reduced environmental impact as well as increased safety for small-scale high-speed synthesis, this protocol is superior to the existing methods or the indenopyridine synthesis.

EXPERIMENTAL

Melting points were determined in a Buchi Melting Point Apparatus and are uncorrected. The ^{1}H- and ^{13}C NMR spectra were run on a Bruker DPX 400 spectrometer operating at 400 MHz and 100 MHz respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The mass-spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) operating at 70 eV. High Resolution Mass Spectra (HRMS) were recorded in a Waters Micromass AutoSpec NT spectrometer (STIUJA). The elemental analyses have been obtained using a LECO CHNS-900 and a Thermo Finnigan FlashEA1112 CHNS-O (STIUJA) elemental analyzers.

General procedure for the synthesis of indeno[1,2-*b*]-pyrazolo[4,3-*e*]pyridines (4a-i). A solution of 5-amino-3-methyl-1-phenylpyrazole **1** (1 mmol), benzaldehyde **2** (1 mmol) and 1,3-indandione **3** (1 mmol) in dimethylformamide (10 mL) containing a catalytic amount of triethylamine was heated under reflux for 6-8 h. The resulting solid product was collected by filtration, washed with ethanol, dried and finally recrystallized from dimethylformamide.

3-Methyl-1,4-diphenylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4a). This compound was obtained according to general procedure as pale yellow crystals. Mp 220-221 °C, yield 58 %. MS (70eV) m/z (%): 388 (26), 387 (100, M^+), 372 (6, M^+ - CH_3^-), 77 (7). HRMS (EI): $C_{26}H_{17}N_3O$ requires: 387.1382; found: 387.1372.

4-(4-Methylphenyl)-3-methyl-1-phenylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4b). This compound was obtained according to general procedure as pale yellow crystals. Mp 217-218 °C, yield 52%. MS (70eV) m/z (%): 402 (29), 401 (100, M^+), 386 (29, M^+ - CH_3^-). Anal. Calcd for $C_{27}H_{19}N_3O$: C, 80.78; H, 4.47; N, 10.47. Found: C, 80.37; H, 4.77; N, 10.57.

4-(4-Methoxyphenyl)-3-methyl-1-phenylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4c). This compound was obtained according to general procedure as pale yellow crystals. Mp 224-225 °C, yield 47%. MS (70eV) m/z (%):419 (5), 418 (36), 417 (100, M^+), 416 (24), 402 (4, M^+-CH_3^-), 386 (6, M^+-OCH_3^-). Anal. Calcd for $C_{27}H_{19}N_3O_2.1/2H_2O$: C, 76.04; H, 4.73; N, 9.85. Found: C, 75.82; H, 4.70; N, 10.03

4-(4-Fluorophenyl)-3-methyl-1-phenylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4d). This compound was obtained according to general procedure as pale yellow crystals. Mp 255-257 °C, yield 54%. MS (70eV) m/z (%): 406 (36), 405 (100, M^+), 404 (41), 390 (15, M^+-CH_3^-). Anal. Calcd for $C_{26}H_{16}FN_3O.1/3H_2O$: C, 75.90; H, 4.08; N, 10.21. Found: C, 76.11; H, 3.86; N, 9.87.

4-(4-Trifluoromethylphenyl)-3-methylphenyl-1*H*-indeno-[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4e). This compound was obtained according to general procedure as pale yellow crystals. Pf 280-281 °C, 51% de rendimiento. MS (70eV) m/z (%): 456 (29), 455 (100, M^+), 454 (18), 440 (4, M^+-CH_3^-), 386 (3, M^+-CF_3^-). Anal. Calcd for $C_{27}H_{16}F_3N_3O.1/3H_2O$: C, 70.28; H, 3.64; N, 9.11. Found: C, 70.36; H, 3.32; N, 9.09

4-(4-Chlorophenyl)-3-methyl-1-phenylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4f). This compound was obtained according to general procedure as pale yellow crystals. Mp 269-270 °C, yield 49%. MS (70eV) m/z (%): 423 (36), 422 (29), 421 (100, M^+), 420 (22), 406 (5, M^+-CH_3^-), 386 (10, M^+-Cl^-). Anal. Calcd for $C_{26}H_{16}ClN_3O.1/3H_2O$: C, 72.98; H, 3.93; N, 9.82. Found: C, 72.77; H, 4.04; N, 9.91.

4-(4-Bromophenyl)-3-methyl-1-phenylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4g). This compound was obtained according to general procedure as pale yellow crystals. Mp 274-276 °C, yield 69%. MS (70eV) m/z (%): 468 (23), 466 (100), 468 (42), 465 (77, M^+), 386 (24, M^+-Br^-), 385 (13). Anal. Calcd for $C_{26}H_{16}BrN_3O.1/2\ H_2O$: C, 65.70; H, 3.60; N, 8.84. Found: C, 65.83; H, 3.24; N, 9.02.

4-(2-Fluorophenyl)-3-methyl-1-phenylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4h). This compound was obtained according to general procedure as pale yellow crystals. Mp 247-249 °C, yield 58%. MS (70eV) m/z (%): 406 (23), 405 (97, M^+), 385 (23), 357 (14), 77 (100), 51 (10). HRMS (EI): $C_{26}H_{16}FN_3O$ requires: 405.1277; found: 405.1277.

3-Methyl-4-(3,4-methylendioxyphenyl)-1-phenylindeno[1,2-*b*]pyrazolo[4,3-*e*]pyridin-5(1*H*)-one (4i). This compound was obtained according to general procedure as pale yellow crystals. Mp 223-224 °C, yield 68%. MS (70eV) m/z (%): 432 (30), 431 (100, M^+), 401 (10), 91 (11), 77 (100), 51 (10). HRMS (EI): $C_{27}H_{17}N_3O_3$ requires: 431.1264; found: 431.1270.

Acknowledgement. Authors are grateful to COLCIENCIAS, to Universidad del Valle, to the Spanish "Consejeria de Innovacion, Ciencia y Empresa, Junta de Andalucia" and Servicios Tecnicos de la Universidad de Jaen (STIUJA). SC thanks to Universidad de Nariño for fellowship.

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