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Regioselective synthesis of fused benzopyrazolo[3,4-*b*]quinolines under solvent-free conditions

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Abstract—New 6,8-dihydro-5*H*-benzo[*f*]pyrazolo[3,4-*b*]quinolines **6** have been obtained in a novel solvent-free three-component reaction involving β-tetralone along with 5-aminopyrazoles **1** and benzaldehydes **2**. The isomeric 6,10-dihydro-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinolines **9** could not be prepared in a similar fashion directly from α-tetralone, but were obtained by the reaction of amines **1** with benzylidene-derivative **10** of α-tetralone in similar conditions. The yields of quinolines obtained via this novel protocol were good and the reaction times varied from few minutes to just few seconds.

1. Introduction

At the dawn of this century, green chemistry has become a major driving force for organic chemists to develop environmentally benign routes to a myriad of materials.[1] For example, the possibility of performing multi-component reactions under solvent-free conditions to enhance the reaction efficiency from both economic and ecological points of view has given to this kind of procedures a remarkable synthetic value and received a great attention.[1b]

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 the starting materials.[2] The huge interest for such multi-component reactions during the last years has been oriented towards developing combinatorial chemistry procedures, because of their high efficiency and convenience of these reactions in comparison with multistage procedures. Hence, most of the scientific efforts have been focused on the development of multi-component procedures to prepare diverse heterocyclic compound libraries.[2b]

Pyrazolo[3,4-*b*]quinoline derivatives have been studied as antiviral[3] and potential antimalarial agents;[4] and some exhibit parasiticide properties[5] and bactericidal activity;[6] some others have been used as vasodilators[7] and have even been evaluated for enzymatic inhibitory activity.[8]

We have concentrated much of our recent work in the preparation of such bioactive nitrogen-containing heterocycles, and have already described simple and efficient procedures to prepare interesting molecules with biological properties as pyrazolo[3,4-*b*]quinolines **4** in a three-component reaction from 5-aminopyrazoles **1**, aromatic aldehydes **2** and dimedone **3**[9] (Scheme 1).

We describe here the preparation, through solvent-free procedures, of two isomeric tetracyclic analogues of pyrazolo[3,4-*b*]quinolines **4** involving, for the first time, the corresponding tetralone instead of dimedone **3**.

2. Results and discussion

The preparation of benzo[*f*]pyrazolo[3,4-*b*]quinoline **6** through a simple three-component solvent-free reaction of 5-aminopyrazoles **1**, benzaldehydes **2** and β-tetralone

Keywords: 5-Aminopyrazole; α-Tetralone; β-Tetralone; Benzaldehyde; Benzopyrazolo[3,4-*b*]quinoline; Three-component reaction; Solvent-free procedure.
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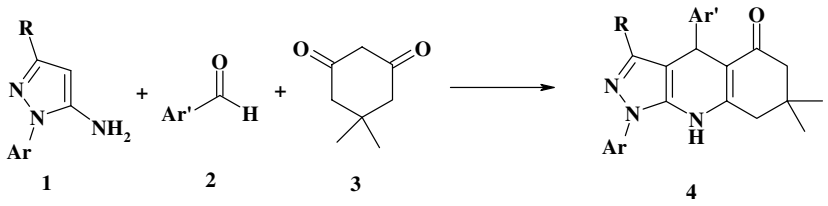


Scheme 1.

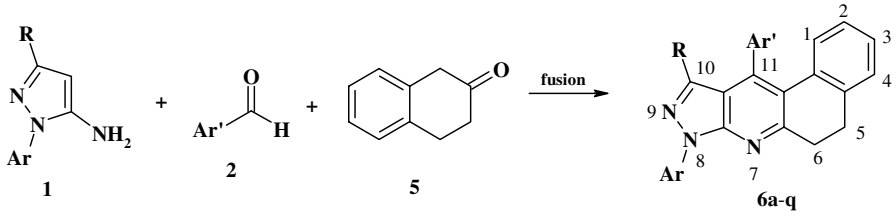
5 was accomplished by fusion procedure (Scheme 2 and Table 1).[10]

The first attempt to provide the benzo[*h*]-analogues **9** was carried out under similar conditions, reacting aminopyrazoles **1**, benzaldehydes **2** and α-tetralone **7** but the unexpected bis-pyrazolopyridines **8** were formed (Scheme 3). This result agrees with the lower reactivity of the active methylene at α-tetralone with respect to the β-tetralone. The optimization of the process to **8** was achieved by the reaction of aminopyrazoles **1** with benzaldehydes **2**.[11]

According to the above results, for the synthesis of 5,10-dihydro-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinolines **9**, α-tetralone benzylidene-derivatives **10** should be previously prepared.[12] Then, interaction of aminopyrazoles **1** with equimolar amounts of benzylidenetetralones **10** in an oil-bath and without solvent yielded the expected products **9a–q** in acceptable to good yields[13] (Scheme 3 and Table 1).

Syntheses of compounds **6** and **9** were also carried out by classic heating in ethanol in order to demonstrate the success of this method. Thus, the heating of equimolar amount of precursors **1**, **2** and **5** for 10–12 h rendered compounds **6** in 40–45% yield, while compounds **9** were obtained in 38–44% yield from aminopyrazoles **1** and benzylidene-derivatives **10** by heating during 20–22 h.

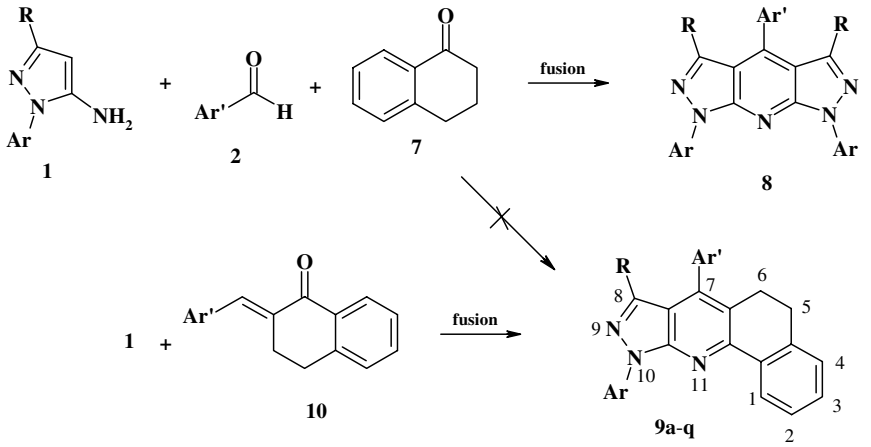
The structures of all new compounds were appropriately established by the usual spectroscopic methods. Single crystal X-ray diffraction analysis of some selected compounds was used to corroborate the postulated structures.[14]



Scheme 2.

Table 1. Benzopyrazolo[3,4-*b*]quinolines **6a–q** and **9a–q** in solvent-free conditions

Entry	R	Ar	Ar′	Compound **6**			Compound **9**		
				Mp (°C)	Yield (%)	rt (min)	Mp (°C)	Yield (%)	rt (min)
a	CH_3	C_6H_5	4-FC_6H_4	208–209	74	1.5	227–228	70	1.5
b	CH_3	C_6H_5	C_6H_5	164–165	50	1.5	221–222	70	1.5
c	CH_3	C_6H_5	4-ClC_6H_4	193–194	50	1.5	195–196	55	1.5
d	CH_3	C_6H_5	4-BrC_6H_4	171–172	54	1.5	207–208	70	1.5
e	CH_3	C_6H_5	4-$CF_3C_6H_4$	187–188	52	1.5	212–213	68	1.5
f	CH_3	C_6H_5	4-$CH_3C_6H_4$	157–158	74	1.5	211–212	80	1.5
g	CH_3	C_6H_5	4-$CH_3OC_6H_4$	148–149	65	1.5	211–212	67	1.5
h	CH_3	C_6H_5	4-Pyridyl	219–220	52	1.5	285–286	60	1.5
i	CH_3	C_6H_5	3-Pyridyl	172–173	54	1.5	201–202	60	1.5
j	CH_3	4-ClC_6H_4	C_6H_5	126–128	51	5.0	195–197	70	3.5
k	CH_3	4-ClC_6H_4	4-$CH_3C_6H_4$	198–200	50	5.0	205–207	72	3.5
l	CH_3	4-ClC_6H_4	4-ClC_6H_4	235–237	57	5.0	251–253	76	3.0
m	CH_3	4-ClC_6H_4	4-BrC_6H_4	243–245	56	5.0	239–241	75	3.0
n	CH_3	4-ClC_6H_4	4-$CH_3OC_6H_4$	188–190	48	5.0	218–220	68	3.5
o	$(CH_3)_3C$	C_6H_5	4-$CH_3C_6H_4$	118–120	48	7.0	174–176	68	3.5
p	$(CH_3)_3C$	C_6H_5	4-ClC_6H_4	170–172	50	6.5	195–197	72	3.5
q	$(CH_3)_3C$	C_6H_5	4-BrC_6H_4	190–192	52	6.5	230–232	72	3.5



Scheme 3.

3. Conclusion

We can conclude that the reported one-step procedure is an efficient, simple and very regioselective alternative for the preparation of benzopyrazolo[3,4-*b*]quinolines via cyclocondensation reactions in solvent-free conditions. The lower reactivity of α-tetralone compared to that of the β-tetralone is reflected by the fact that α-tetralone does not participate in a three-component reaction. Alternatively, in order to obtain compounds **9**, previous formation of intermediate **10** from the reaction of α-tetralone with the aldehydes is necessary. Prominent among the advantages of this new method are operational simplicity, good yields, short reaction times and easy work-up.

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10. *Preparation of 6,8-dihydro-5H-benzo[f]pyrazolo[3,4-b]-quinolines* (**6a**–**q**): A mixture of equimolar amounts of corresponding 5-aminopyrazoles **1** (2 mmol), benzaldehydes **2** (2 mmol) and β-tetralone **5** (2 mmol) was thoroughly mixed at room temperature. The mixture was heated in an oil-bath at 120 °C for 1.5–7 min. It was then stirred and allowed to cool to room temperature when it solidified. The solid material was treated with ethanol and recrystallized from DMF. Data for 11-(4-fluorophenyl)-10-methyl-8-phenyl-5,8-dihydro-5*H*-benzo[*f*]pyrazolo[3,4-*b*]-quinoline **6a**: White crystal, mp 208–209 °C, (74%). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.95$ (s, 3H, CH_3), 2.93 (t, 2H, CH_2, C5), 3.11 (t, 2H, CH_2, C6), 6.81 (d, 1H, CH, C1), 6.84 (t, CH, C3), 7.08 (t, CH, C2), 7.28 (d, CH, C4), 7.29, 7.56, 8.30 (5H; *p*, *m*, *o*-Ph, respectively), 7.30 (d, 2H, H*m*) 7.42 (d, 2H, H*o*); RMN ^{13}C (DMSO-d_6): $\delta = 13.9$ (CH_3), 28.1 (CH_2, C5), 33.9 (CH_2, C6), 114.9 (C10a), 119.9 (C*o*-Ph), 122.3 (C11a) 124.8 (C*p*-Ph) 124.9 (C3), 126.3 (C2), 127.1 (C4), 128.1 (C1), 115.1 (C*m*), 128.5 (C*m*-Ph), 131.2 (C*o*) 162.8 (C*p*), 131.2 (C*i*), 138.7 (C11b), 143.6 (C11), 138.8 (C*i*-Ph), 140.5 (C4a), 142.4 (C10), 148.3 (C7a), 160.9 (C6a); MS: (30 eV) *m*/*z* (%) = 405 (100, M^+), 390 (7). HRMS (EI): $C_{27}H_{20}FN_3$ requires: 405.1641; found: 405.1699.
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13. *Preparation of 6,10-dihydro-5H-benzo[h]pyrazolo[3,4-b]-quinolines* (**9a**–**q**): A mixture of 5-aminopyrazole **1** (2 mmol) and benzylidene-derivative of α-tetralone **10**[12]

(2 mmol) was thoroughly mixed at room temperature. The mixture was heated in an oil-bath at 120 °C for 1.5–3.5 min. It was then stirred and allowed to cool to room temperature when it solidified. The solid material was treated with ethanol and recrystallized from DMF. Data for 7-(4-fluorophenyl)-8-methyl-10-phenyl-5,10-dihydro-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline **9a**: White crystal, mp 227–228 °C, (70%). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.03$ (s, 3H, CH_3), 2.78 (t, 2H, CH_2, C6), 2.86 (t, 2H, CH_2, C5), 7.24 (d, 1H, CH, C4), 7.23 (d, 2H, H*m*), 7.31 (d, 2H, H*o*), 7.27, 7.54 and 8.44 (5H; *p*, *m*, *o*-Ph, respectively), 7.36 (t, CH, C3), 7.42 (t, CH, C2), 8.51 (d, CH, C1); RMN ^{13}C (DMSO-d_6): $\delta = 14.5$ (CH_3), 22.2 (CH_2, C6), 28.6 (CH_2, C5), 115.6 (C7a), 121.3 (C*o*-Ph), 125.9 (C*p*-Ph), 129.7 (C*m*-Ph), 140.8 (C*o*-Ph), 124.9 (C6a), 127.2 (C1) 128.0 (C2), 128.5 (C4), 131.5 (C*o*), 116.2 (C*m*), 133.0 (C*i*), 165.0 (C*p*), 130.5 (C3), 135.9 (C11b), 140.0 (C4a), 143.0 (C7), 143.3 (C8), 150.9 (C10a), 153.5 (C11a); MS: (30 eV) m/z (%) = 405 (100, M^+), 360 (5). HRMS (EI): $C_{27}H_{20}FN_3$ requires: 405.1641; found: 405.1666.

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