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Multicomponent approaches to 8-carboxylnaphthyl-functionalized pyrazolo[3,4-*b*]pyridine derivatives†

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A simple and novel protocol for the efficient synthesis of a series of 8-carboxylnaphthyl functionalized pyrazolo[3,4-*b*]pyridine derivatives was developed through a one-pot, three-component reaction involving acenaphthylene-1,2-dione and 1*H*-pyrazol-5-amine in acetic acid medium. The reaction represents the first facile conversion of acenaphthenequinone to naphthoic acid *via* C–C bond cleavage without need for multi-step transformation.

The pyrazolo[3,4-*b*]pyridine ring system[1] is present in a number of pharmaceutically important compounds targeted, for instance, to inhibit (or potentially inhibit) glycogen synthase kinase-3 (GSK-3),[2] xanthine oxidases,[3] cholesterol formation,[4] A1 adenosine receptors,[5] phosphodiesterase 4 (PDE4) in immune and inflammatory cells,[6] p38 as anti-inflammatory drugs,[7] and to treat Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and alcohol withdrawal symptoms, drug addiction and infertility.[8] Naphthoic acid is also a key motif which often occurs in several biologically active natural products and pharmaceutical compounds,[9–13] and its derivatives have been reported to play a vital role in the development of new drugs against several human ailments and infectious diseases.[14–17] Functionalization of naphthoic acid at the 8-position with macrocycles such as porphyrin exhibited interesting properties. Chang *et al.* disclosed that Co(II) 1-naphthylporphyrin-substituted with a carboxyl group at the 8-naphthyl position displayed significant enhancement in O_2 affinity.[18] Unmetallated *trans*-porphyrin bearing two 8-carboxyl-functionalized naphthalene spacers represented a unique example of a reversible, redox-controlled porphyrin-porphodimethane interconversion *via* a sequential intramolecular ring opening and closure reaction.[19] In comparison to the case of macrocycles, introduction of other heterocyclic systems into the 8-position of naphthoic acid has rarely been investigated.[20] Taking these facts into account, we conceived that molecules bearing both pyrazolo[3,4-*b*]pyridine and naphthoic acid units would be applicable as potential multifunctional materials. Nevertheless, the preparation of these compounds still remained unknown.

In recent years, much attention has been paid to the modification and synthesis of the pyrazolo[3,4-*b*]pyridine scaffold for drug discovery purposes.[21] The main strategies for the construction of pyrazolo[3,4-*b*]pyridines were focused on the three-component reaction of 5-aminopyrazoles, *aldehydes* and appropriate cyclic ketones by various methods.[22] Because 8-formyl-1-naphthoic acid is not readily available, functionalization at the 8-position of naphthoic acid is often accessed by using acenaphthenequinone as a precursor *via* multi-step transformation.[23] Recently, we found that three-component reaction of acenaphthylene-1,2-dione, 1*H*-pyrazol-5-amines and ketones could be performed facilely in acetic acid to provide the 8-carboxylnaphthyl-functionalized pyrazolo[3,4-*b*]pyridine derivatives. To the best of our knowledge, the reaction was the first synthesis of 8-heterocycle-functionalized naphthoic acid in a one-pot, cascade manner. Herein, we report these results.

Our studies commenced with the reaction of 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile (**1b**), acenaphthylene-1,2-dione (**2**) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3b**) in HOAc medium at 120 °C. In our previous work, three-component reaction of **1b**, **3b** and isatin in HOAc/H_2O solvent was found to produce spirooxindole derivatives.[24] Similar results were observed as well by Shi *et al.* in the reaction of **2**, **3b** and 1,3-dicarbonyl compounds.[25] So, our initial attempt for the selected reaction was to generate spiro-compound **4′** (Scheme 1). However, unexpectedly, a new product different from **4′** was obtained. All the analytical data showed that the three reactants were all included in the formation of final product, producing a novel naphthoic acid functionalized with pyrazolo[3,4-*b*]pyridine, **4b** (Scheme 1). The definite structure of **4b** was further confirmed by X-ray single crystal analysis (Fig. 1).[26] This surprising result is of value to us not only because we are interested in the design of the new three-component reaction[27] but also because we were unable to find examples of other methods allowing for such convenient synthesis of pyrazolo[3,4-*b*]pyridines simultaneously containing naphthoic acid and indole units in the related literature.

Encouraged by the result, we next made an effort to optimize the reaction conditions. It was found that in HOAc medium, lowering the reaction temperature led to inhibition of the reaction and thus a relatively poor yield of product (Table 1, entries 1–3). Other protic solvents such as EtOH, H_2O were examined as well under refluxing condition. However, no desired reaction was observed

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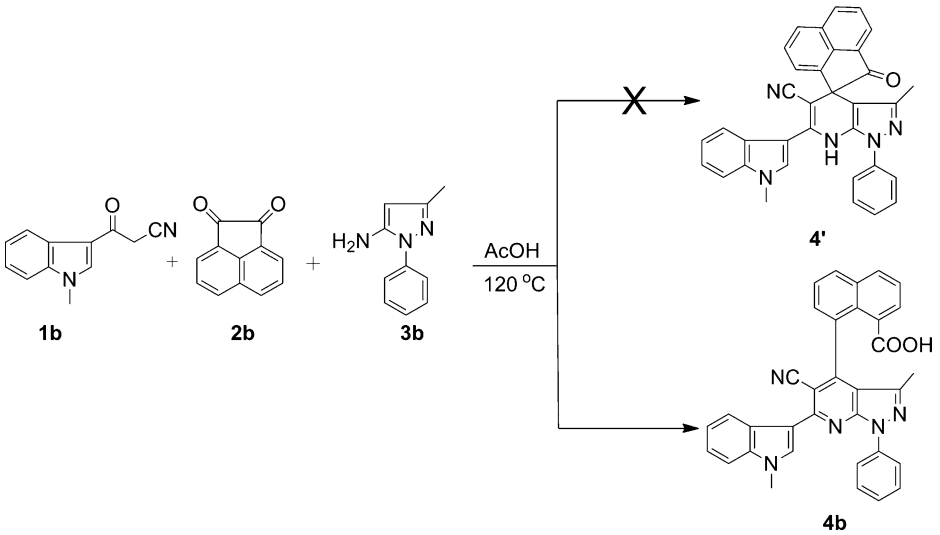


Scheme 1 An unexpected formation of product **4b**.

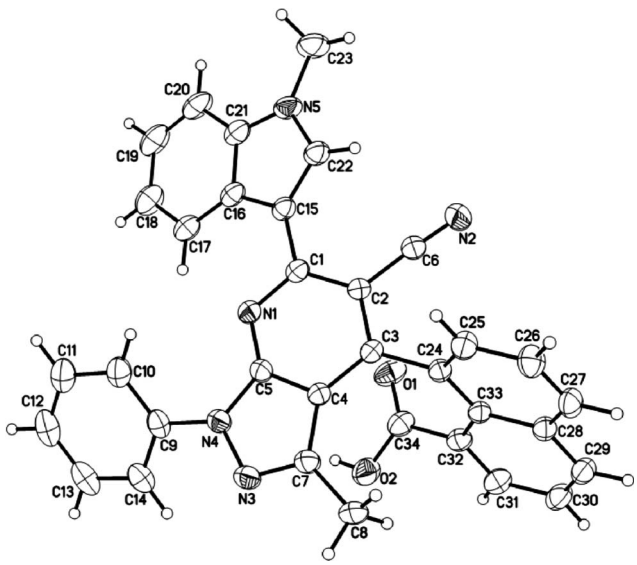


Fig. 1 X-Ray crystal structure of product **4b**.

Table 1 Optimization of reaction conditions[a]

Entry	Solvent[b]	*T*/°C	Time/h	Yield (%)[c]
1	**AcOH**	**120**	**8**	**76**
2	AcOH	100	20	54
3	AcOH	80	36	26
4	EtOH	80	48	0
5	H_2O	100	24	0
6[d]	EtOH	80	48	0
7[d]	H_2O	100	24	0
8[d]	DMF	155	24	complex mixture
9[d]	CH_3CN	80	24	complex mixture

[a] Molar ratio **1b**:**2**:**3b** = 1:1:1. [b] 4 mL solvent was used. [c] Isolated yield. [d] These reactions were carried out in the presence of 30 mol% *p*-toluenesulfonic acid.

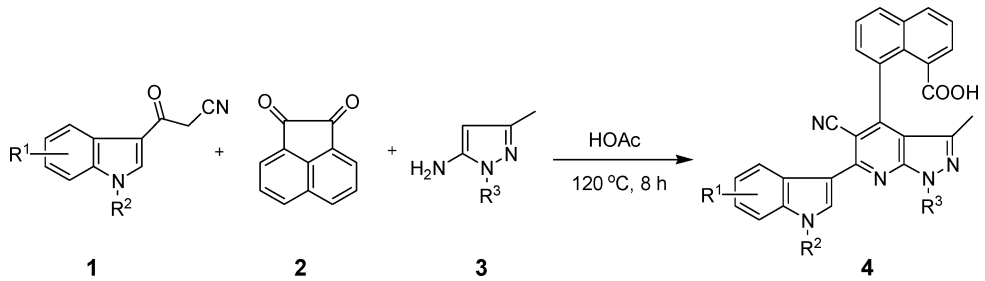
under the conditions (Table 1, entries 4–5). Then we turned our attention to the use of Brønsted acid catalysis. When 30 mol% *p*-toluenesulfonic acid was added to the reaction mixture in EtOH or H_2O, respectively, no expected reaction occurred (Table 1, entries 6–7). Aprotic solvents including DMF and acetonitrile were also employed in the presence of 30 mol% *p*-toluenesulfonic acid, but the reactions were messy which resulted in complex mixtures which were impossible to separate into analytically pure products (Table 1, entries 8–9).

Having established the optimal conditions (120 °C, HOAc), we subsequently investigated the substrate scope of the transformation. As shown in Table 2, substituents such as methyl, bromo, methoxycarbonyl, benzyl in the indole ring, and phenyl and methyl in the pyrazole ring, were well tolerated in the reactions, leading to the final products in satisfactory yields (up to 85%). To our surprise, when 3-methyl-1*H*-pyrazol-5-amine (R^3 = H), one candidate in the compound **3** series, was introduced in the reaction, no positive outcome was returned. Under the standard conditions, 3-methyl-1*H*-pyrazol-5-amine remained intact and only condensation between **1** and **2** occurred. We supposed that the lower electronic density of the pyrazole ring might result in its weak nucleophilicity. Thus, 3-methylisoxazol-5-amine was selected as an analog of **3** for further inspection; however, no promising result was obtained under optimal conditions.

On the basis of the experiments, a possible mechanism was proposed for the formation of **4** as shown in Scheme 2. First, condensation of **1** and **2** occurred to generate the intermediate A. Then, intermolecular Michael addition of **3** to A, followed by an intramolecular nucleophilic cyclization *via* B, led to the formation of C. After elimination of water, D was thus produced. In the presence of an oxidant such as oxygen, D was oxidized and converted to product **4**.

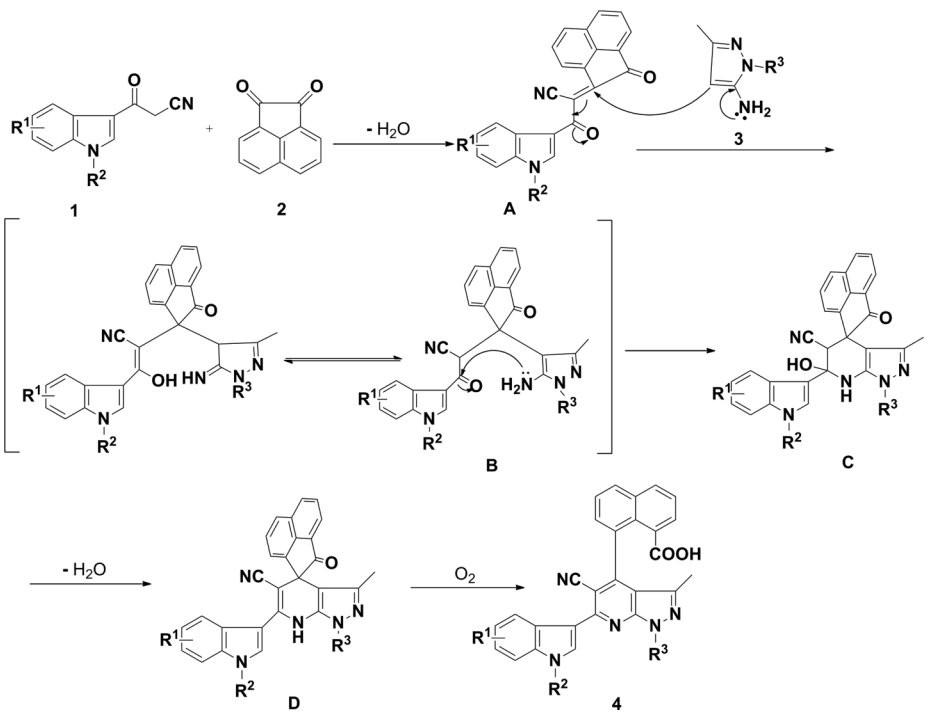
After successful access to the indole containing pyrazolo[3,4-*b*]pyridine-functionalized naphthoic acid, our curiosity was turned to seeking substitutes for **1** for wider generality of the reaction. It was fortunately found that a 1,3-dicarbonyl compound and its analog were also proven to be good candidates for this transformation. Two representative examples are listed in Scheme 3. The yields of desired products were higher than those with **1** as reactant.

Table 2 Substrate scope study[a]



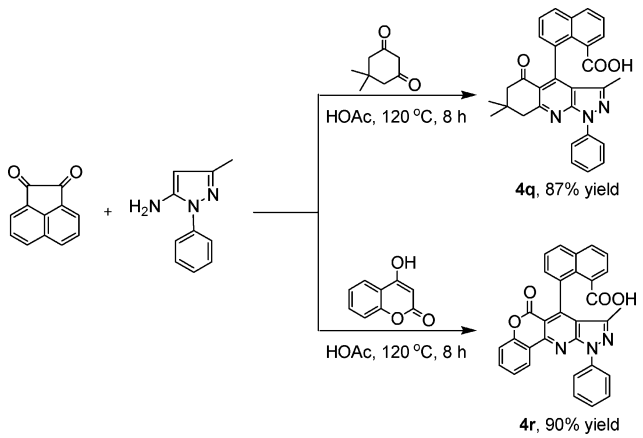
Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	H	H	Ph	**4a**	72
2	H	Me	Ph	**4b**	76
3	4-Me	H	Ph	**4c**	62
4	5-Me	H	Ph	**4d**	70
5	6-Me	H	Ph	**4e**	75
6	7-Me	H	Ph	**4f**	72
7	H	H	Me	**4g**	76
8	H	Me	Me	**4h**	71
9	5-Me	H	Me	**4i**	78
10	6-Me	H	Me	**4j**	70
11	7-Me	H	Me	**4k**	73
12	5-Br	H	Ph	**4l**	85
13	5-Br	H	Me	**4m**	80
14	H	Bn	Ph	**4n**	82
15	H	Bn	Me	**4o**	75
16	4-COOMe	H	Ph	**4p**	70

[a] Molar ratio **1** : **2** : **3** = 1 : 1 : 1. [b] Isolated yield.



Scheme 2 A possible mechanism for the formation of **4**.

In conclusion, we have developed a novel and efficient approach to 8-carboxylnaphthyl-functionalized pyrazolo[3,4-*b*]pyridine derivatives *via* a one-pot, three-component condensation involving acenaphthylene-1,2-dione and 1*H*-pyrazol-5-amine in HOAc medium. It was the first direct conversion of acenaphthenequinone to a naphthoic acid fragment *via* C–C bond cleavage without the need for multi-step transformation. An overall study concerning the impact of structural and functional motifs on the reaction is currently in progress in our laboratory.



Scheme 3 Synthesis of **4q** and **4r** using 1,3-dicarbonyl compounds as substrates.

Acknowledgements

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26 Crystallographic data for the structure of **4b**·DMF reported in this paper have been deposited at the Cambridge Crystallographic Data Centre with No. CCDC 844424. Structural parameters for **4b**·DMF: data collection: Rigaku Mercury CCD area detector; crystal size: 0.60 × 0.50 × 0.20 mm^3; $C_{37}H_{30}N_6O_3$, M_r = 606.67, monoclinic, space group $P21/c$, a = 11.3442(11), b = 19.9830(18), c = 13.8952(13) Å, α = 90.00, β = 99.660(3), γ = 90.00°, V = 3105.3(5) Å^3, Z = 4, D_c = 1.298 g cm^{-3}, $R_{[I > 2\sigma(I)]}$ = 0.0789, $wR_{[I > 2\sigma(I)]}$ = 0.1621.
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