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Study on the iodine-catalyzed reaction of 3-aminopyrazine-2-carbohydrazide and 2-(arylethynyl)benzaldehydes

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ABSTRACT

At 60 °C in DMSO, the iodine-catalyzed reaction of 3-aminopyrazine-2-carbohydrazide and 2-(arylethynyl)benzaldehydes led hydrazones. Increasing the reaction temperature to 100 °C, the amino and amido still indicated inactive, only the imine took part in the addition of acetylene bond to give 2-arylisoquinolines in high yields with the cleavage of N-N bond unexpectedly under metal-free conditions.

1. Introduction

Isoquinoline is a very useful heterocyclic skeleton, and the derivatives of which possess various kinds of pharmacological and biological activities, such as anti-telomerase,[1] anti-tobacco mosaic virus,[2] antibacterial,[3] and anti-muscle atrophy activities.[4] *Roxadustat* (FG-4592; Fig. 1, left)[5] is a well-known drug based on isoquinoline moiety, and it is an anti-anemic drug which is already used in the phase III clinical trials. Another medicine is the famous *Papaverine*[6] (Fig. 1, right) which is also a polysubstituted isoquinoline. It is an opium alkaloid and antispasmodic medication which is used in the treatment of visceral spasm and vasospasm. In view of their biological applications, numerous novel procedures have been reported to synthesize structurally diversified isoquinoline derivatives in recent years.[7]

Of which, utilization of 2-(arylethynyl)benzaldehyde as a reactant is a very efficient method to construct 2-substituted isoquinolines. The nitrogen sources involve NH_4OAc,[8] NH_4HCO_3,[9] amidine,[10] urea,[11] hydrazine,[12] NH_3,[13] amine[14] and hydroxylamine.[15] However, the catalyst of transition metal salt is essential to this conversion because it is always used to activate carbon-carbon triple bond, such as Cu(I),[10] Cu(II)[11] and Yb(III),[16] especially for Ag(I).[8,9,12,14,15] Therefore, searching for a novel procedure under metal-free conditions is still necessary.

Iodine is a mild Lewis acid which has been used to promote a lot of organic reactions.[17] In our recent study, it was submitted to catalyze the reaction of 3-aminopyrazine-2-carbohydrazide (**1**) and 2-(arylethynyl)benzaldehydes (**2**) in the air. Our intention was to build the fused tetracyclic 5-arylidene-5,6-dihydro-8*H*-phthalazino [1,2-*b*]pteridin-8-ones using three amino groups in the reactant of **1**. However, the amino on pyrazine and the amido group all showed chemical inertness, only the third hydrazine amino group took part in the reaction. It was found that only hydrazones were obtained at 60 °C, while at 100 °C, the subsequent cyclization and cleavage of N-N bond took place to give 2-arylisoquinolines losing a molecule of 3-amino-*N*-hydroxypyrazine-2-carboxamide unexpectedly (Scheme 1).

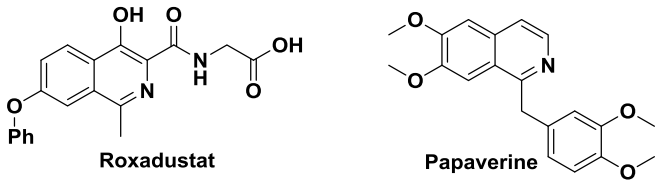

Fig. 1. The drugs containing isoquinoline moiety.

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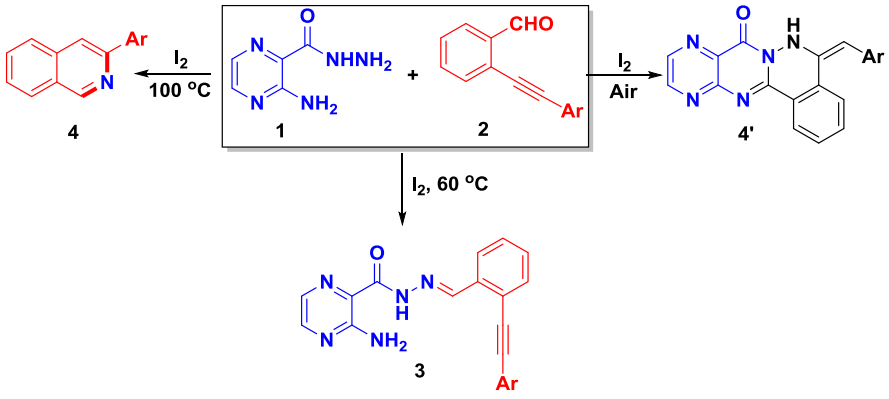
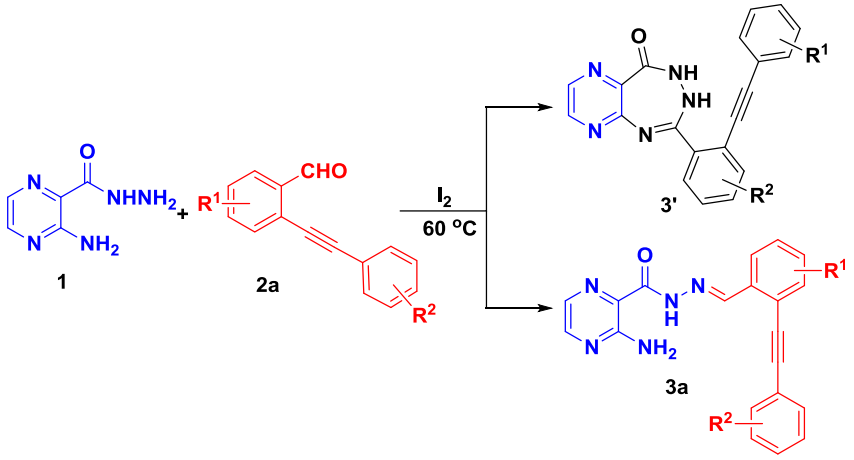


Scheme 1. Our approach to 2-arylisoquinolines.



Scheme 2. The iodine-catalyzed reaction to hydrazone at 60 °C.

As our continuous research on the construction of heterocycles catalyzed by iodine,[18] we would like to report the synthesis of 2-arylisoquinolines from an iodine-catalyzed reaction of 3-aminopyrazine-2-carbohydrazide and 2-(arylethynyl) benzaldehydes under metal-free conditions.

2. Results and discussion

As shown in Schemes 1 and 2, in our initial assumption, we planned to build phthalazino[1,2-*b*]pteridin-8-one skeleton promoted by iodine. However, a new compound was obtained at 60 °C in the presence of 5 mol% iodine, and twelve protons (see SI) were observed in its ^{1}H NMR when 2-(phenylethynyl)benzaldehyde (**2a**, $R^1 = R^2 = H$) was submitted to react with **1** in DMSO. Two peaks arriving (see SI) at 86.2 and 95.1 indicated that the triple bond did not attend the reaction initially. According to the NMR data, 5*H*-pyrazino[2,3-*e*][1,2,4]triazepin-5-one (**3′**) was thought to be the cyclation and oxidation product. Subsequently, various kinds of **2** (Table 1) were tested to react with **1**, and all gave the similar products **3a**-**m** in high yields under the optimized reaction conditions. In our continuous study, a single crystal of **3e** was obtained in $CHCl_3$ solution, and the X-ray diffraction analysis (Fig. 2) confirmed that it was the hydrazone (**3e**) that was 3-amino-*N*'-(5-fluoro-2-(phenylethynyl) benzylidene)pyrazine-2-carbohydrazide.

In order to promote one of the following reactions: (1) the addition of amino and imine; (2) the coupling between amido and triple bond of carbon; (3) the addition of imine and acetylenic bond, we subsequently changed the reaction temperature, catalyst dosage and solvents in our lab (Table 2). It was found that the third addition of imine and acetylenic bond gradually took place when the reaction increased to 100 °C giving isoquinoline derivatives. Furthermore, the highest yield reached 91% using 10 mol% iodine as a catalyst (Table 2) in the solvent of DMSO.

With the optimized reaction conditions in hand, we next investigated the substrate scope of the I_2-catalyzed reaction by varying 2-(arylethynyl)benzaldehydes (Table 3). In general, the

Table 1
The synthetic results for the products **3**.

Entry	R^1	R^2	Products	Yields (%)
1	H	H	**3a**	95
2	4-Cl	H	**3b**	97
3	4-F	H	**3c**	93
4	5-Cl	H	**3d**	97
5	5-F	H	**3e**	92
6	5-OCH_3	H	**3f**	93
7	4,5-$(OCH_3)_2$	H	**3g**	90
8	2-Thienyl	H	**3h**	91
9	H	3-Cl	**3i**	92
10	H	4-Cl	**3j**	85
11	4-Cl	3-F	**3k**	89
12	4,5-$(OCH_3)_2$	4-Cl	**3l**	88
13	4,5-$(OCH_3)_2$	4-*n*-Pr	**3m**	87

Reaction condition: **1** (77 mg, 0.5 mmol), **2** (0.5 mmol), iodine (7 mg), DMSO (5.0 mL), 60 °C.