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Domino Approach for the Synthesis of Pyrrolo[1,2-α]pyrazine from Vinyl Azides

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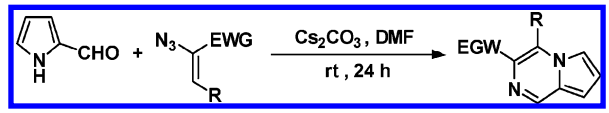
ABSTRACT



A domino synthesis of pyrrolo[1,2-α]pyrazine from 1*H*-2-pyrrolecarbaldehyde and readily synthesized vinyl azides was developed. This reaction proceeded under relatively mild conditions in the presence of base. Additionally, a possible mechanism for the entire sequence is proposed.

The pyrrolo[1,2-α]pyrazine is a privileged heterocyclic scaffold. Some pyrrolo[1,2-α]pyrazine derivatives exhibit neuroleptic and cardiovascular activity.[1,2] The range of physiological activities has led to an array of synthetic procedures for the preparation of pyrrolo[1,2-α]pyrazine. Over the past decades, some of the most common synthetic methodologies reported in the literature include $TiCl_4$-stereoselective 6-exo-dig cyclization of 2-acetyl-*N*-propargylpyrrole,[3] $POCl_3$-catalyzed condensation of pyrrolacetal,[4] oxidation of the 3,4-dihydropyrrolo[1,2-a]pyrazine,[5] and direct derivation of the parent pyrazine.[6] However, some of the common synthetic approaches are limited by either their low yields, harsh experimental conditions, or substrate complexity. In light of this, a general and straightforward methodology to rapidly prepare structurally diverse pyrrolo[1,2-α]pyrazine is still in demand.

Vinyl azide is a pivotal three-atom synthon for the formation of nitrogen-containing heterocycles (azaheterocycles). In recent years, novel synthetic strategies exploiting vinyl azide have emerged from the literature.[7−9] Therefore, in principle vinyl azides might serve as a source of three atoms when 2-pyrrolecarbaldehyde is used as a nucleophilic attacker[7d] to initiate a domino process for the generation of molecular complexity.[10] In this communication, we present a general and simple nucleophilic domino reaction to provide the pyrrolo[1,2-α]pyrazine from vinyl azids in the presence of base.

The reaction of vinyl azide, derived from 4-bromobenzaldehyde, with 1*H*-2-pyrrolecarbaldehyde was selected as a prototype reaction (Table 1). No reaction was observed without any additive (Table 1, entry 1), but the transformation occurred in the presence of a variety of bases at 25 °C to form **3** as the major product (Table 1). Screening of bases revealed Cs_2CO_3 as the most efficient base (Table 1, entries 3−7). Optimization of solvent showed that DMF (Table 1, entry 2) was superior to other aprotic and protic solvents (Table 1, entries 8−11). The reaction was also assessed at a

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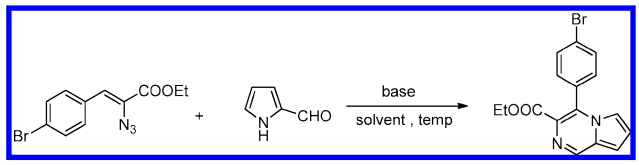
Table 1. Optimization of Reaction Conditions[a]



entry	base	solvent	t (°C)	conversion[b] (%)
1	–	DMF	25	n.r.
2	**Cs_2CO_3**	**DMF**	**25**	**88**
3	K_2CO_3	DMF	25	31
4	NaH	DMF	25	80
5	*t*-BuOK	DMF	25	63
6	CH_3ONa	DMF	25	51
7	DBU	DMF	25	28
8	Cs_2CO_3	DCM	25	n.r.
9	Cs_2CO_3	EtOH	25	n.r.
10	Cs_2CO_3	dioxane	25	n.r.
11	Cs_2CO_3	CH_3CN	25	47
12	Cs_2CO_3	DMF	40	80

[a] Reaction conditions: vinyl azide (0.2 mmol, 1.0 equiv), 1*H*-pyrrole-2-carbaldehyde (0.22 mmol, 1.1 equiv), base (0.22 mmol, 1.1 equiv), 2 mL of solvent, 24 h, rt. [b] Determined by high-performance liquid chromatography, based on the disappearance of the starting vinyl azide. The most successful entry is highlighted in bold.

higher temperature (Table 1, entry 12) but with a slight decrease in the yield. On the basis of this initial study, the optimal reactivity was obtained in DMF at 25 °C when Cs_2CO_3 was employed (88%, Table 1, entry 2).

With the optimized reaction conditions in hand, the scope of the reaction was studied using a set of vinyl aizdes **1** and 1*H*-2-pyrrolecarbaldehyde **2**. The vinyl azides (entries 1−12) were readily prepared from the corresponding benzaldehydes with ethyl 2-azidoacetate via Knoevenagel condensation,[7] and other vinyl azides (entries 13−18) were prepared from the corresponding olefins by successive reaction with bromine then with sodium azide,[11] respectively.

As presented in Table 2, various substituted vinyl azides with 1*H*-2-pyrrolecarbaldehyde worked well to provide the corresponding pyrrolo[1,2-a]pyrazine in moderate to good isolated yields. The reaction could tolerate aromatic substituted vinyl azides with various steric and electronic properties (Table 2, entries 1−11).

Notably, vinyl azides bearing an electron-withdrawing group at the aryl ring gave the desired products with good efficiency (>70%) after only 8 h at 25 °C. The retarding effect of sterics on the reaction is illustrated in entry 4 where ortho substituents on the aryl ring gave slightly reduced yield (68%), compared to entry 3 (72%).

Instead of α-ethoxycarbonyl-substituted vinyl azides, the reaction of vinyl azide (Table 2, entries 13 and 14) bearing an arylcarbonyl group at the α-position gave the desired products with lower yields (<60%), and the reaction of α-azidostyrene (Table 2, entry 15) was sluggish, requiring higher temperature and longer reaction time.

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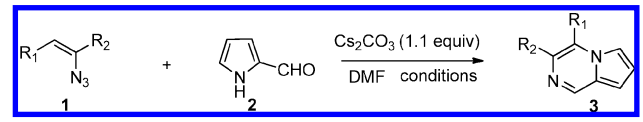
Table 2. Cyclization of 1*H*-Pyrrole-2-carbaldehyde with Various Vinyl Azides[a]

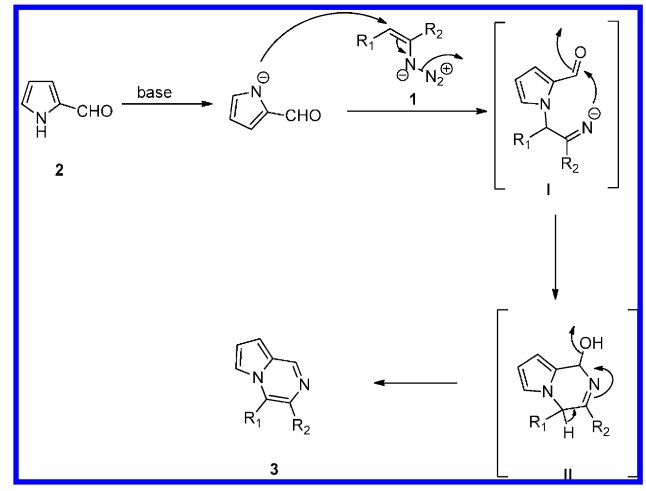


entry	R_1	R_2	product **3**	yield (%)[b]
1	Ph	CO_2Et	**3a**	62
2	4-$MeOC_6H_4$	CO_2Et	**3b**	61
3	4-BrC_6H_4	CO_2Et	**3c**	72
4	2-BrC_6H_4	CO_2Et	**3d**	68
5	4-FC_6H_4	CO_2Et	**3e**	77
6	3-$NO_2C_6H_4$	CO_2Et	**3f**	74
7	furyl	CO_2Et	**3g**	59
8	4-$PhCH_2OC_6H_4$	CO_2Et	**3h**	61
9	4-MsC_6H_4	CO_2Et	**3i**	66
10	3,4-di-ClC_6H_3	CO_2Et	**3j**	72
11	3,4-$(OCH_2O)C_6H_3$	CO_2Et	**3k**	69
12	2,3,4-tri-FC_6H_2	CO_2Et	**3l**	71
13[c]	4-BrC_6H_4	COPh	**3m**	58
14[c]	4-BrC_6H_4	4-Cl-PhCO	**3n**	60
15[d]	H	Ph	**3o**	57
16	H	1-(morpholinyl)-CO	**3p**	92
17	Ph	CHO	**3q**	51
18[e]	Ph	H	**3r**	n.r.

[a] Reactions were performed in anhydrous DMF at rt with 1.1 equiv of 1*H*-pyrrole-2-carbaldyhyde **2** under N_2 atomsphere. [b] Isolated yield. [c] The reaction was performed at −30 °C for 5 h. [d] The reaction was performed at 50 °C for 24 h. [e] *E*:*Z* = 1:1.

Whereas treatment of vinyl azide (Table 2, entry 17), with a strong electron-withdrawing group, gave the product in lower yield (51%, Table 2, entry 17), α-*N*-morpholinylcarbonyl-substituted vinyl azide greatly accelerated this process, providing the corresponding product in higher yield (92%, Table 2, entry 16). The problem was considered to be the instability of the vinyl azides in the reaction conditions.

Scheme 1. Proposed Mechanism for the Synthesis of Pyrrolo[1,2-α]pyrazine



β-Azidostyrene (Table 2, entry 18), however, was detrimental to the desired transformation. Therefore, this new reaction constitutes an efficient and simple way to carry out the formation of pyrrolo[1,2-a]pyrazine. This synthetic transformation is nontrivial and requires several steps in other methodologies.

On the basis of the results presented above, we proposed the following possible mechanism for this reaction, as shown in Scheme 1. First, it is expected to involve Michael addition−elimination of the pyrrole **2** to the vinyl azides **1** affording an active intermediate **I**, driven by the excellent leaving-group ability of nitrogen. Subsequently, the reaction undergoes an intramolecular condensation to give the desired product **3**.

In conclusion, we have developed a new, mild strategy to prepare functionalized pyrrolo[1,2-a]pyrazine. This reaction was realized through a novel domino process from readily available vinyl azides and 1*H*-2-pyrrolecarbaldehyde. Such a domino process includes a Michael addition and subsequent intramolecular condensation at room temperature and moreover it is economical in atom count as only a molecule of nitrogen and water is lost in the entire process.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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