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Pyridine Group-Assisted Addition of Diazo-Compounds to Imines in the 3-CC Reaction of 2-Aminopyridines, Aldehydes, and Diazo-Compounds

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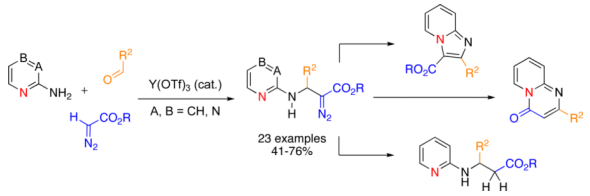
Abstract



A novel three-component (3-CC) coupling reaction of 2-aminoazines, aromatic aldehydes and diazo-compounds producing polyfunctional β-amino-α-diazo-compounds has been developed. The reaction features an unprecedented heterocycle-assisted addition of a diazo-compound to an imine. The obtained diazoesters were efficiently converted into valuable heterocycles, as well as to β-amino acid derivatives.

Nucleophilic addition of diazo-compounds to activated imines bearing strong electron-withdrawing groups at the nitrogen atom represents an important method of C–C bond formation, employed in the synthesis of β-amino acid derivatives, as well as other valuable products (Scheme 1, eq 1).[1,2] Thus, Wang and co-workers reported a base-promoted reaction of *N*-SO_2R imines with diazoesters producing β-amino-α-diazocarbonyl compounds.[3] On the other hand, Terada, Maruoka, and others reported Brønsted acid-catalyzed addition of diazo-compounds to *N*-COAr and *N*-Boc imines (eq 1).[4] However, these efficient methods are limited to activated imines only.

Herein we report an efficient Lewis acid-catalyzed addition of diazoesters to pyridine-containing imines **1** producing β-amino-α-diazocarbonyl compounds **2** (eq 2).[5] Moreover, we also developed a 3-CC reaction of 2-aminoazines, aldehydes and diazo-compounds to form **2**. The obtained β-amino-α-diazoesters represent useful synthetic scaffolds, which can be efficiently converted into diversely substituted heterocycles, such as imidazo[1,2-a]pyridine, pyrido[1,2-a]pyrimidine-4-one, as well as to *N*-pyridyl substituted β-amino acids.

In continuation of our studies[6] toward a multi-component synthesis of heterocycles,[7] we explored a three-component coupling reaction of 2-aminopyridine, an aldehyde, and a

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Supporting Information Available Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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diazoester. It was found that the reaction of imine of 2-aminopyridine **1a** with ethyl diazoacetate in the presence of Py•TfOH (10 mol %) produced diazo-compound **2a**[8] along with some amounts of enamine **3a**, a product of the 1,2-aryl shift (Table 1, entry 1).[9] We considered this outcome quite interesting, as it represents the first efficient[5] addition of diazo-Accordingly, optimization studies toward a more efficient formation of **2** were performed.

It was found that strong acids such as TfOH (entry 2), as well as Tf_2NH (entry 3), can catalyze this reaction to produce **2a**, together with a by-product enamine **3a**. Employment of weaker acids, such as CF_3CO_2H (entry 4), did not give any product, whereas the use of phenylphosphinic acid catalyst produced the product **2a** selectively, though in moderate yield only (entry 5). We found that the reaction of *tert*-Bu and *c*-Hex-diazoacetates afforded products **2b** and **2c**, respectively, in slightly better yield. However, formation of significant amounts of enamine **3** was observed (entries 6, 7). To our delight, the amount of enamine by-product **3** was significantly decreased when lanthanide triflates were used (entries 8-11). After this two-component coupling (2-CC) reaction was optimized, we aimed at the development of a more synthetically attractive 3-CC reaction. We found that this transformation, can indeed be performed in a three-component fashion starting from an aldehyde, a 2-aminopyridine, and a *c*-Hex diazoacetate which forms the product **2c** in high yield (entry 12).

With optimized conditions in hand, we explored the scope of this novel 3-CC reaction. Thus, aromatic aldehydes bearing electron-donating and neutral groups (Table 2, entries 1-7), at the *o*-, *m*-, and *p*- positions reacted smoothly. Benzaldehydes having electron-withdrawing groups, such as fluoro (entry 8), bromo (entries 9,10), NO_2 (entry 12), and CF_3 (entry 13), produced the corresponding diazo esters in slightly lower yields (entries 8-13). In addition, an aldehyde bearing an unprotected hydroxy group (entry 11), as well as a heteroaromatic aldehyde, such as 2-thiophenecarboxaldehyde (entry 14), were tolerated under these reaction conditions. Substituted 2-aminopyridines were also competent partners for this 3-CC reaction (entries 15-18). However, the reaction of 2-aminopyridine, having an electron-withdrawing group, afforded the product in diminished yield (entry 18). The reaction could also be performed with other 2-aminoazines, namely 2-aminopyrimidine (entry 19), and 2-aminopyrazine (entry 20), as well as with 2-aminothiazole (entry 21), producing the corresponding products in reasonable yields. In addition to diazoesters, diethyl (diazomethyl)phosphonate can also be employed to form the corresponding β-amino-α-diazo-compounds **2v,w** efficiently (entries 22 and 23). In general, the reaction shows high functional group tolerance with respect to all three components. Notably, aryl amines without a nitrogen atom at the α-position of the ring, such as aniline as well as 3- and 4-aminopyridines, do not produce detectable amounts of the corresponding diazo-products (entry 24).[10]

We rationalize these observations in the following way (Scheme 2). First, the formed Y(III)-activated imine **A** undergoes a nucleophilic attack by the diazo-compound to produce zwitter-ion **B/C**. It is likely that the nitrogen atom of pyridine ring serves as an intramolecular proton shuttle. Thus, deprotonation in **B/C** by the pyridine *N*-atom leads to diazo-intermediate **D**, producing diazo-compound **2** upon release of Y(III)-catalyst and tautomerization process. Therefore, the overall process can be considered as a pyridine group-assisted addition of diazo-compounds to imines. This mechanism is in good agreement with the fact that aniline, as well as 3- and 4-aminopyridines, which do not possess a properly situated *N*-atom, do not undergo this addition reaction (Table 2, entry 24).[10]

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The obtained azine-containing β-amino-α-diazo-compounds **2** represent a versatile scaffold for various types of transformations. Thus, exploring the carbene reactivity of the obtained molecules, we found that diazoester **2c** (R = CO_2*c*-Hex) could undergo a selective 1,2-hydride shift[11] in the presence of $AgBF_4$ (5 mol %) to produce enamine 4.[12] Interestingly, the corresponding α-diazoethylposphonate **2v** (R = $PO(OEt)_2$), under these reaction conditions, underwent an exclusive 1,2-aryl shift to form the enamine product **5**.[3c]

In addition, hydrogenation of the diazo-group of **2c** efficiently converted it to β-amino acid derivative **6**. The synthetic usefulness of the diazo-compounds **2** was further demonstrated in an efficient one-pot synthesis of *N*-fused heterocycles via cyclization of the in situ formed enamine **4**. Thus, in the presence of $La(OTf)_3$, it underwent lactamization into pyrido[1,2-a]pyrimidine-4-one **7**. On the other hand, NIS-mediated cyclization converted **4** into imidazo[1,2-a]pyridine **8** (Scheme 3). Presumably, the cyclization of **4** into **8** proceeds via intramolecular attack of the pyridine nitrogen at the double bond of the enamine activated by an electrophilic agent, followed by a subsequent elimination and a tautomerization processes (Scheme 4).

In conclusion, we have developed a novel three-component coupling reaction of 2-aminoazines, aromatic aldehydes, and diazo compounds producing β-amino-α-diazoesters. This reaction features an unprecedented heterocycle-assisted addition of a diazocompound to an imine. The obtained β-amino-α-diazoesters represent an important polyfunctional synthetic scaffold suitable for useful transformations. Thus, the obtained diazo--compounds could be efficiently converted into valuable heterocyclic molecules such as imidazo[1,2-a]pyridines and pyrido[1,2-a]pyrimidine-4-ones, as well as β-(2-pyridyl)-amino acid derivatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. See Supporting Information for full optimization results.

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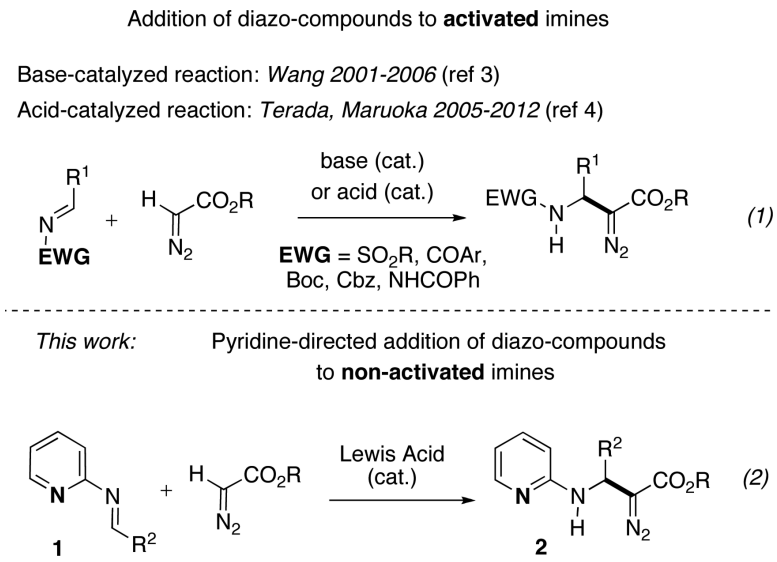

Scheme 1.

Pyridine-directed addition of diazo-compounds to imines

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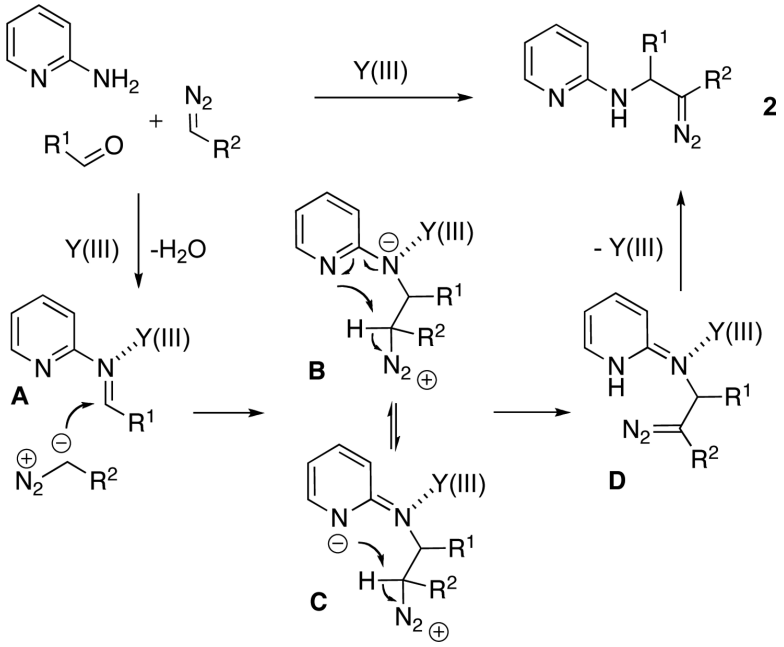
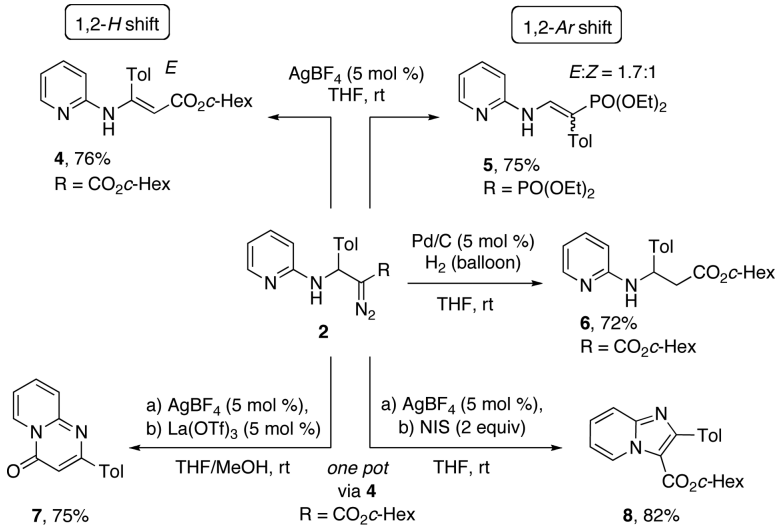


Scheme 2.
Proposed mechanism of new 3-CC reaction



Scheme 3.

Synthetic applications of diazocompounds **2**

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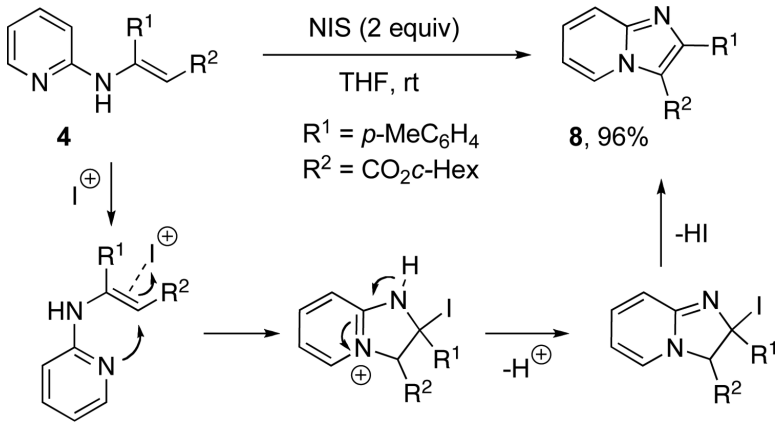

Scheme 4.

The proposed mechanism for formation of **8**

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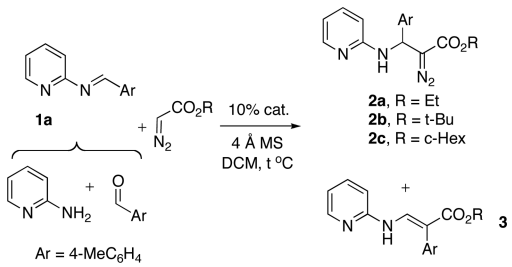
Table 1

Optimization of the new 3-CC reaction conditions[a]



entry	catalyst	R	t °C	2	3
1[b]	Py•TfOH	Et	rt	56%	15%
2[b]	TfOH	Et	rt	45%	15%
3[b]	Tf_2NH	Et	rt	55%	15%
4[b]	CF_3CO_2H	Et	rt	-	-
5[b,c]	$PhP(OH)_2$	Et	rt	50%	2%
6[b]	Py•TfOH	*t*-Bu	rt	59%	14%
7[b]	Py•TfOH	*c*-Hex	rt	63%	13%
8[b]	$Sc(OTf)_3$	*c*-Hex	rt	42%	14%
9[b]	$La(OTf)_3$	*c*-Hex	rt	63%	10%
10[b]	$Y(OTf)_3$	*c*-Hex	rt	52%	1%
11[b]	$Y(OTf)_3$	*c*-Hex	10 °C	15%	3%
12[d]	$Y(OTf)_3$	*c*-Hex	10 °C	14%	4%

[a]NMR yields after 24 h.

[b]2-CC reaction of imine **1a** with diazocomponds.

[c]Toluene was used as a solvent.

[d]3-CC reaction from 2-aminopyridine, *p*-tolualdehyde, and *c*-Hex diazoacetate.

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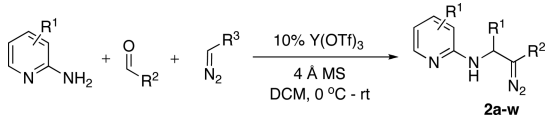
Table 2

The scope of the new 3-CC reaction[a]



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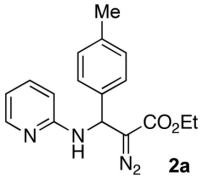
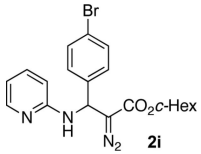
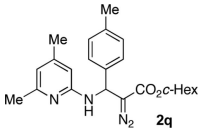
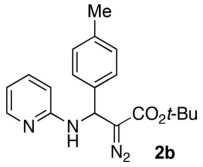
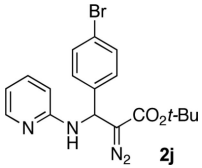
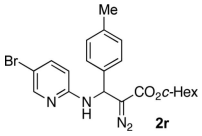
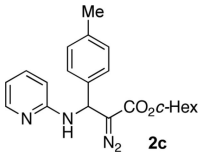
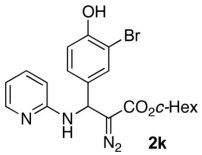
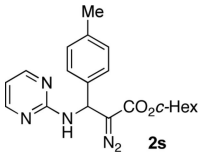
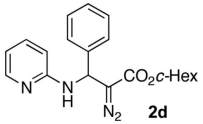
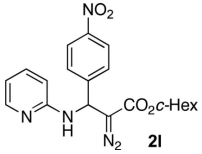
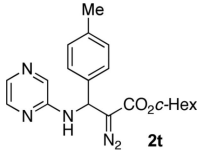
1	 **2a**	60	9	 **2i**	65	17	 **2q**	50
2	 **2b**	64	10	 **2j**	62	18[b]	 **2r**	45
3	 **2c**	70	11	 **2k**	51	19	 **2s**	42
4	 **2d**	71	12[b]	 **2l**	50	20	 **2t**	46

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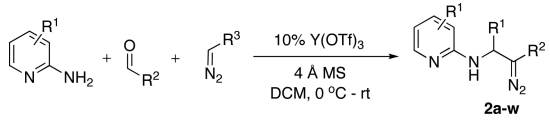

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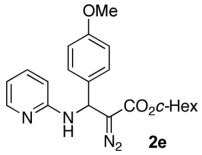
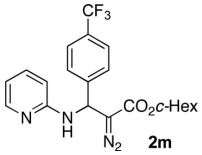
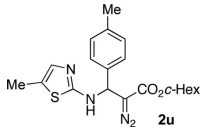
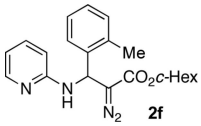
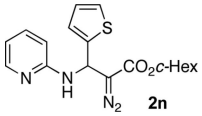
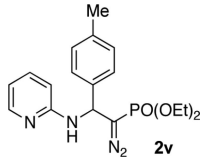
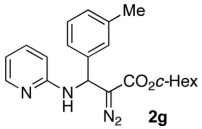
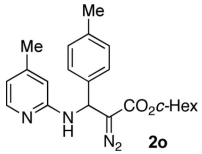
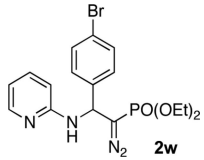
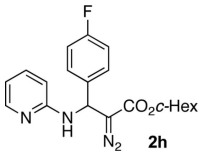
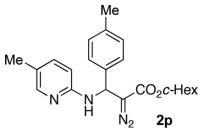
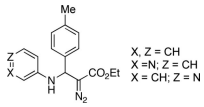
5		60	13		68	21		41
6		66	14		45	22		67
7		76	15		75	23		51
8		58	16		63	24		-[c]

[a]Unless otherwise noted: aldehyde (1 equiv), 2-aminoazine (1.1 equiv), diazo-compound (1.2 equiv), Y(OTf)3 (10%) and MS 4 Å (125 mg/mmol) in CH_2Cl_2 (0.3 M).

[b]Pre-formed imine was used.

[c]See ref 10.