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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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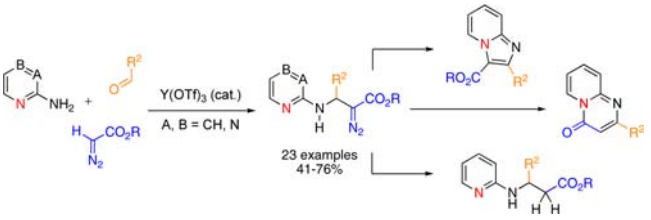
ABSTRACT



A novel three-component coupling (3-CC) 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 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] 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 and pyrido[1,2-*a*]pyrimidine-4-one, as well as into *N*-pyridyl substituted β-amino acids.

In continuation of our studies[6] toward a multicomponent synthesis of heterocycles,[7] we explored a three-component

(1) For selected recent reviews on reactivity of diazo-compounds, see: (a) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162. (b) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (e) Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, *617–618*, 98.

(2) For a recent review on reactions of diazo-compounds as nucleophiles, see: Zhang, Y.; Wang, J. *Chem. Commun.* **2009**, 5350.

(3) For base-promoted addition of diazo-compounds to activated imines, see: (a) Jiang, N.; Qu, Z.; Wang, J. *Org. Lett.* **2001**, *3*, 2989. (b) Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285. (c) Zhao, Y.; Jiang, N.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 8339. (d) Chen, S.; Zhao, Y.; Wang, J. *Synthesis* **2006**, 1705. For a diastereoselective reaction, see: (e) Zhao, Y.; Ma, Z.; Zhang, X.; Zou, Y.; Jin, X.; Wang, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5977.

(4) For enantioselective acid-catalyzed addition of diazo-compounds to activated imines, see: (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. (b) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (c) Maruoka, K.; Hashimoto, T. *Synthesis* **2008**, 3703. (d) Hashimoto, T.; Kimura, H.; Nakatsu, H.; Maruoka, K. *J. Org. Chem.* **2011**, *76*, 6030. (e) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, *3*, 642. (f) Zhang, H.; Wen, X.; Gan, L.; Peng, Y. *Org. Lett.* **2012**, *14*, 2126. For heterogeneous catalysis of this reaction, see: (g) Kantam, M. L.; Balasubrahmanyam, V.; Kumar, K. B. S.; Venkanna, G. T.; Figueras, F. *Adv. Synth. Catal.* **2007**, *349*, 1887.

(5) A single example of a low efficiency (24% yield) Ag-mediated addition of ethyl diazoacetate to a nonactivated imine was reported: Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 8084.

(6) (a) Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2743. (b) Chernyak, D.; Chernyak, N.; Gevorgyan, V. *Adv. Synth. Catal.* **2010**, *352*, 961.

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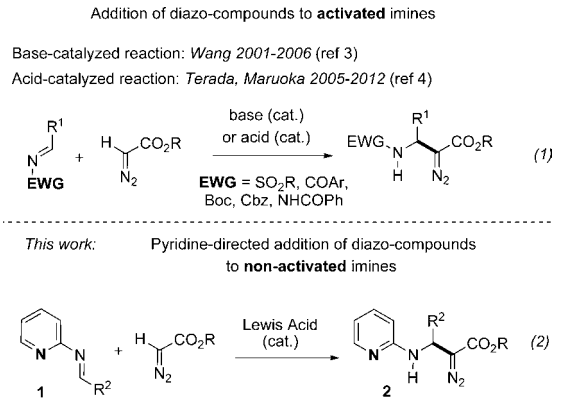
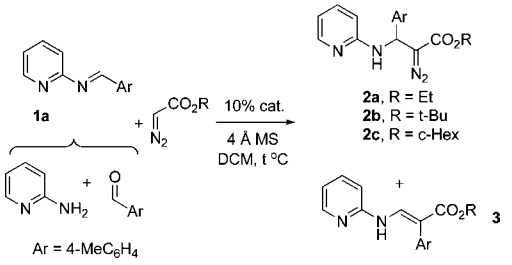
Scheme 1. Pyridine-Directed Addition of Diazo-Compounds to Imines



coupling reaction of a 2-aminopyridine, an aldehyde, and a diazoester. It was found that the reaction of the 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 to be quite interesting, as it represents the first efficient[5] addition of diazo-compounds to an imine that does not possess a strong electron-withdrawing group at the N-atom.

Table 1. Optimization of the New 3-CC Reaction Conditions[a]



entry	catalyst	R	*t*	**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	75%	3%
12[d]	$Y(OTf)_3$	*c*-Hex	10 °C	74%	4%

[a] NMR yields after 24 h. [b] 2-CC reaction of imine **1a** with diazo-compounds. [c] Toluene was used as a solvent. [d] 3-CC reaction from 2-aminopyridine, *p*-tolualdehyde, and *c*-Hex diazoacetate.

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 byproduct enamine **3a**. Employment of weaker acids, such as CF_3CO_2H (entry 4), did not give any product, whereas the use of a 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 yields. However, formation of significant amounts of enamine **3** was observed (entries 6, 7). To our delight, the amount of enamine byproduct **3** was significantly decreased when lanthanide triflates were used (entries 8–11). After this two-component coupling (2-CC) reaction was optimized, we focused on 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).

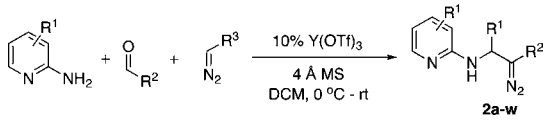
With optimized conditions in hand, we explored the scope of this novel 3-CC reaction. Thus, aromatic aldehydes bearing electron-donating and -neutral groups (Table 2, entries 1–7) at the *o*-, *m*-, and *p*-positions reacted smoothly. Benzaldehydes having electron-withdrawing groups, such as fluoro (entry 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 a 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

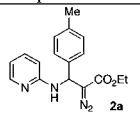
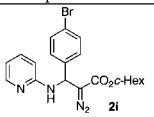
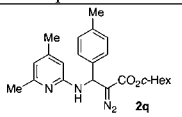
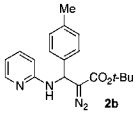
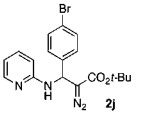
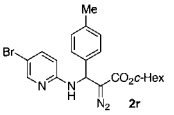
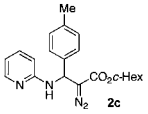
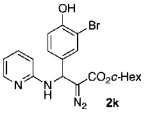
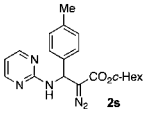
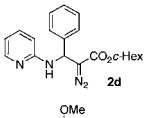
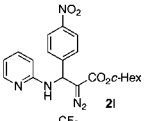
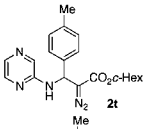
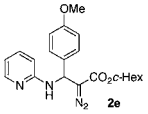
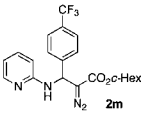
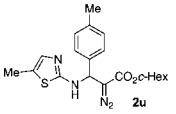
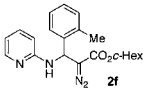
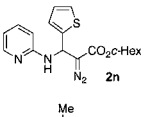
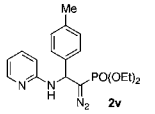
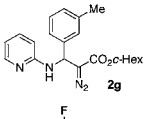
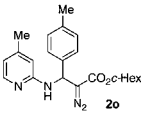
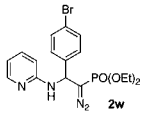
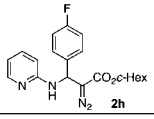
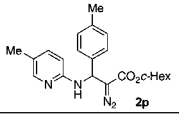
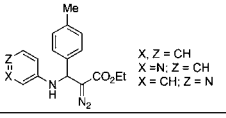
(7) For selected reviews on multicomponent coupling reactions, see: (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: 2005. (b) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234. (c) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. (d) *Synthesis of Heterocycles via Multicomponent Reactions I, II*; Orru, R. V. A., Ruijter, E., Eds.; Topics in Heterocyclic Chemistry; Springer, Vol. 23, 2010.

(8) The X-ray analysis of the product **2j** confirmed the presence of the diazo-group in the obtained products (see Supporting Information for details). CCDC-916523 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(9) Notably, the likely aza-Darzens aziridination reaction of imine was not observed. For Py•TfOH-catalyzed aziridination of imines with diazocompounds, see: (a) Bew, S. P.; Carrington, R.; Hughes, D. L.; Liddle, J.; Pesce, P. *Adv. Synth. Catal.* **2009**, *351*, 2579. For $Ln(OTf)_3$-catalyzed aziridination of imines with diazocompounds, see: (b) Nagayama, S.; Kobayashi, S. *Chem. Lett.* **1998**, 685. (c) Xie, W.; Fang, J.; Li, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929.

Table 2. Scope of the New 3-CC Reaction[a]



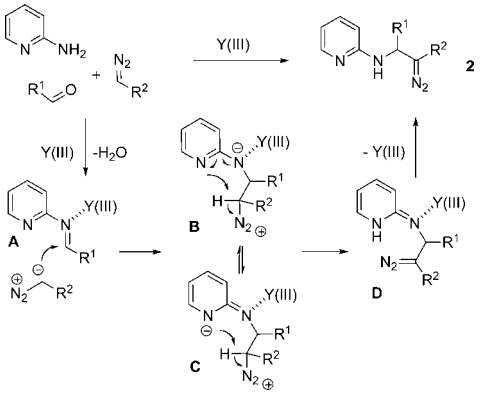
entry	product	yield (%)	entry	product	yield (%)	entry	product	yield (%)
1	 **2a**	60	9	 **2i**	65	17	 **2q**	50
2	 **2b**	64	10	 **2j**	62	18[b]	 **2r**	45
3	 **2c**	70	11	 **2k**	51	19	 **2s**	42
4	 **2d**	71	12[b]	 **2l**	50	20	 **2t**	46
5	 **2e**	60	13	 **2m**	68	21	 **2u**	41
6	 **2f**	66	14	 **2n**	45	22	 **2v**	67
7	 **2g**	76	15	 **2o**	75	23	 **2w**	51
8	 **2h**	58	16	 **2p**	63	24	 X, Z = CH; X =N; Z = CH; X = CH; Z = N	-[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] Preformed imine was used. [c] See ref 10.

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 zwitterion **B**/**C**. It is likely that the nitrogen atom of the 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 a 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

Scheme 2. Proposed Mechanism of New 3-CC Reaction

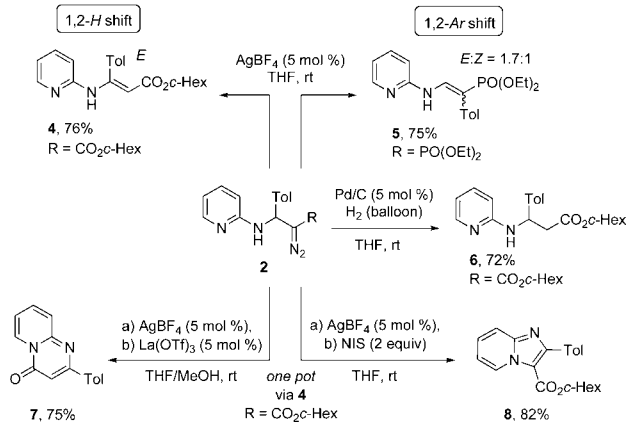


(10) For 3-CC reaction attempts employing aniline as well as 3- and 4-aminopyridines, see Supporting Information.

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]

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_2c-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]

Scheme 3. Synthetic Applications of Diazo-Compounds **2**

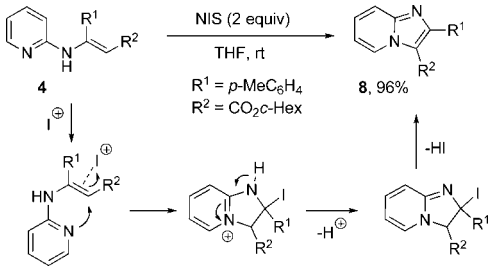


In addition, hydrogenation of the diazo-group of **2c** efficiently converted it to β-amino acid derivative **6**. The synthetic usefulness of the diazo-compounds **2** was further demonstrated in an efficient one-pot synthesis of *N*-fused heterocycles via cyclization of the in situ formed enamine **4**.

(11) For 1,2-migrations in β-amino-α-diazoesters, see: (a) Jiang, N.; Wang, J. *Synlett* **2002**, 149. (b) Jiang, N.; Ma, Z.; Qu, Z.; Xing, X.; Xie, L.; Wang, J. *J. Org. Chem.* **2003**, *68*, 893. (c) Shi, W.; Jiang, N.; Zhang, S.; Wu, W.; Du, D.; Wang, J. *Org. Lett.* **2003**, *5*, 2243. (d) Shi, W.; Xiao, F.; Wang, J. *J. Org. Chem.* **2005**, *70*, 4318. (e) Xu, F.; Zhang, S.; Wu, X.; Liu, Y.; Shi, W.; Wang, J. *Org. Lett.* **2006**, *8*, 3207. (f) Xiao, F.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5789. See also refs 3a, 3c, 3d.

(12) See Supporting Information for full optimization results.

Scheme 4. Proposed Mechanism for Formation of **8**



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 process (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.

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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.

The authors declare no competing financial interest.