## 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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A novel three-component coupling (3-CC) reaction of 2-aminoazines, aromatic aldehydes, and diazo-compounds producing polyfunctional  $\beta$ -amino- $\alpha$ -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  $\beta$ -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  $\beta$ -amino acid derivatives, as well as other valuable products

(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.

(Scheme 1, eq 1).<sup>1,2</sup> Thus, Wang and co-workers reported a base-promoted reaction of N-SO<sub>2</sub>R imines with diazoesters producing  $\beta$ -amino- $\alpha$ -diazocarbonyl compounds.<sup>3</sup> Terada, Maruoka, and others reported Brønsted acid catalyzed addition of diazo-compounds to N-COAr and N-Boc imines (eq 1).<sup>4</sup> 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  $\beta$ -amino- $\alpha$ -diazocarbonyl compounds **2** (eq 2).<sup>5</sup> Moreover, we also developed a 3-CC reaction of 2-aminoazines, aldehydes, and diazo-compounds to form **2**. The obtained  $\beta$ -amino- $\alpha$ -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  $\beta$ -amino acids.

In continuation of our studies<sup>6</sup> toward a multicomponent synthesis of heterocycles,<sup>7</sup> we explored a three-component

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.

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

<sup>(5)</sup> 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.

<sup>(6) (</sup>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.

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**<sup>8</sup> along with some amounts of enamine **3a**, a product of the 1,2-aryl shift (Table 1, entry 1).<sup>9</sup> We considered this outcome to be quite interesting, as it represents the first efficient<sup>5</sup> 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<sup>a</sup>



entry	catalyst	R	t	2	3
$1^b$	Py•TfOH	Et	rt	56%	15%
$2^b$	TfOH	$\mathbf{Et}$	rt	45%	15%
$3^b$	$Tf_2NH$	$\mathbf{Et}$	rt	55%	15%
$4^b$	$CF_3CO_2H$	$\mathbf{Et}$	rt	_	_
$5^{b,c}$	PhP(OH) <sub>2</sub>	$\mathbf{Et}$	rt	50%	2%
$6^b$	Py•TfOH	<i>t</i> -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) <sub>3</sub>	c-Hex	rt	63%	10%
$10^b$	Y(OTf) <sub>3</sub>	c-Hex	rt	52%	1%
$11^b$	Y(OTf) <sub>3</sub>	c-Hex	10 °C	75%	3%
$12^d$	Y(OTf) <sub>3</sub>	c-Hex	10 °C	74%	4%

<sup>*a*</sup>NMR yields after 24 h. <sup>*b*</sup>2-CC reaction of imine **1a** with diazocompounds. <sup>*c*</sup>Toluene was used as a solvent. <sup>*d*</sup>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<sub>2</sub>NH (entry 3), can catalyze this reaction to produce 2a, together with a byproduct enamine 3a. Employment of weaker acids, such as CF<sub>3</sub>CO<sub>2</sub>H (entry 4), did not give any product, whereas the use of a phenylphosphinic acid catalyst produced the product 2a selectively, though in moderate vield 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<sub>2</sub> (entry 12), and CF<sub>3</sub> (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 aldehvde, such as 2-thiophenecarboxaldehvde (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

<sup>(7)</sup> 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.

<sup>(8)</sup> 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.

<sup>(9)</sup> 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)<sub>3</sub>-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<sup>a</sup>





<sup>a</sup> Unless otherwise noted: aldehyde (1 equiv), 2-aminoazine (1.1 equiv), diazo-compound (1.2 equiv), Y(OTf)<sub>3</sub> (10%), and MS 4 Å (125 mg/mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.3 M). <sup>b</sup> Preformed imine was used. <sup>c</sup> See ref 10.

 $\beta$ -amino- $\alpha$ -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  $\alpha$ -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).<sup>10</sup>

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  $\mathbf{B}/\mathbf{C}$ . 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 diazocompound 2 upon release of a Y(III)-catalyst and tautomerization process. Therefore, the overall process can be

Scheme 2. Proposed Mechanism of New 3-CC Reaction



considered as a pyridine group assisted addition of diazocompounds to imines. This mechanism is in good agreement

<sup>(10)</sup> 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).<sup>10</sup>

The obtained azine-containing  $\beta$ -amino- $\alpha$ -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<sub>2</sub>*c*-Hex) could undergo a selective 1,2-hydride shift<sup>11</sup> in the presence of AgBF<sub>4</sub> (5 mol %) to produce enamine **4**.<sup>12</sup> Interestingly, the corresponding  $\alpha$ -diazoethylposphonate **2v** (**R** = PO(OEt)<sub>2</sub>), under these reaction conditions, underwent an exclusive 1,2-aryl shift to form the enamine product **5**.<sup>3c</sup>

Scheme 3. Synthetic Applications of Diazo-Compounds 2 1,2-H shift 1,2-Ar shift <sub>Tol</sub> E *E*:*Z* = 1.7:1 AgBF<sub>4</sub> (5 mol %) THF, rt PO(OEt) H ŕο 4.76% 5.75% R = CO<sub>2</sub>c-He  $R = PO(OEt)_2$ Pd/C (5 mol %) H<sub>2</sub> (balloon) THE rt 6 72% 2 R = CO<sub>2</sub>c-Hex a) AgBF<sub>4</sub> (5 mol %), a) AαBF₄ (5 mol %) b) La(OTf)3 (5 mol %) b) NIS (2 equiv) THF/MeOH, rt THF, rt one po Tol CO<sub>2</sub>c-Hex via 4 R = CO<sub>2</sub>c-Hex 7.75% 8,82%

In addition, hydrogenation of the diazo-group of 2c efficiently converted it to  $\beta$ -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.

Scheme 4. Proposed Mechanism for Formation of 8



Thus, in the presence of La(OTf)<sub>3</sub>, 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  $\beta$ -amino- $\alpha$ -diazoesters. This reaction features an unprecedented heterocycle-assisted addition of a diazocompound to an imine. The obtained  $\beta$ -amino- $\alpha$ -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  $\beta$ -(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.

<sup>(11)</sup> For 1,2-migrations in  $\beta$ -amino- $\alpha$ -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.

<sup>(12)</sup> See Supporting Information for full optimization results.

The authors declare no competing financial interest.