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A New Reactivity Mode of Diazo-Group: Diastereoselective 1,3-Aminoalkylation Reaction of β -Amino- α -Diazoesters Towards Triazolines**

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Abstract

A novel reactivity mode of a diazo-group, the 1,3-addition of a nucleophile and an electrophile to the diazo-group, has been realized in the intramolecular aminoalkylation of β -amino- α -diazoesters to form tetrasubstituted 1,2,3-triazolines. The reaction proved to have a broad scope, good functional group tolerance, and excellent diastereoselectivity. In addition, a new Au-catalyzed intramolecular transannulation reaction of the obtained propargyl triazolines into pyrroles has been discovered.

Keywords

Diazocompound; Triazoline; Heterocycle; Diastereoselective Reaction; Aminoalkylation

Diazocompounds are important building blocks that have been extensively studied over the years.^[1,2] They are widely used in organic chemistry due to the high energy and diverse reactivity of the diazo-group. Primarily, diazocompounds are utilized in denitrogenative generation of metal carbene species.^[3] On the other hand, reactions with preservation of the diazo-group are also known. Thus, [3+2] cycloaddition reactions of diazocompounds are commonly used for synthesis of *N*-heterocycles.^[4] There are also scattered reports on the reaction of nucleophiles and electrophiles with diazo-group in a *1,1-fashion* when both, nucleophile and electrophile are added to the terminal nitrogen atom of the diazo-group. Reactions of this type are limited to the addition of nucleophiles (RLi or hydride ion), followed by protonation, to produce hydrazones (Scheme 1, eq. 1).^[5,6] Herein we disclose a novel reactivity mode of diazocompounds: a *1,3-addition* of nucleophile and electrophile at the nitrogen and carbon atoms of the diazo-group (eq. 2). This reactivity mode was accomplished in highly diastereoselective aminoalkylation reaction of the β -amino- α -diazoesters **1** with alkyl halides furnishing 1,2,3-triazolines **2** (eq. 3).

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Recently, we have developed a method for synthesis of β -pyridylamino- α -diazoesters via a three-component coupling reaction of 2-aminoazines, aldehydes, and diazocompounds (Scheme 2, eq. **a**).^[7] Upon investigation of synthetic utility of the obtained products, we found an unexpected reactivity of the diazo-group. Thus, an alkylation reaction of *N*-pyridyl diazocompound **1aa** with benzyl bromide in the presence of NaH, instead of expected *N*-alkylation product **1'**, produced 1,2,3-triazoline **2a**, the product of *C*-alkylation of diazo-group (Scheme 2, eq. **b**).^[8] This reaction proceeds exclusively in a *trans*-manner with respect to the aryl substituent at the β -position of the diazoester.^[9]

Not only the observed aminoalkylation reaction is interesting conceptually as it represents the first example of intramolecular 1,3-addition of nucleophile and electrophile to the diazo-group, but it also holds a synthetic promise to become a modular approach to valuable 1,2,3-triazoline molecules.^[10] Accordingly, we turned our attention to the investigation of the scope of this new transformation (Table 1). Gratifyingly, we found that this aminoalkylation reaction is quite general with respect to the substituent at the β -*N*-atom of diazoester **1**.

Thus, upon reaction of **1** with benzyl bromide, triazolines bearing pyrimidyl (**2ab**), acetyl (**2ac**), pivaloyl (**2ad**), carboxybenzyl (**2ae**), and *tert*-butoxycarbonyl (**2af**) groups at *N*-atom were formed in high yields and diastereoselectivity (Table 2, entries 1–5). In the case of β -*N*-benzoyl diazoester, the product **2ag** was formed in lower yield and diastereoselectivity (entry 6), whereas β -*N*-tosyl amino and β -*N*-diphenylphosphonyl diazoesters produced the corresponding enamines **1ah'** and **1ai'** as major products (entries 7,8). Next, we examined the scope of alkylating agents in this transformation. It was found that benzyl triflate is also a competitive reaction partner, however the product **2aj** was obtained in a slightly lower yield than in the case of reaction with benzyl bromide (Table 1, entry 9). Benzyl bromides having electron-donating (entries 10–12) or electron-withdrawing groups (entries 13,14), as well as allyl bromide (entries 15–17), also underwent aminoalkylation reaction with different diazocompounds producing the desired products in high yields. This reaction also works with internal (entries 18–24) and terminal (entry 25) propargyl bromides, as well as with methyl bromoacetate (entry 26) and bromoacetonitrile (entry 27) as alkylating agents. Notably, simple aliphatic alkylating agents, such as methyl iodide (entries 28–30), *n*-butyl iodide, as well as *n*-butyl bromide (entry 31), efficiently participated in the aminoalkylation reaction. Notably, secondary alkyl halides (entries 31–33) produced the corresponding triazolines in good yields. The reaction showed good tolerance with respect to the electronic properties of the aryl substituent and *N*-pyridyl group of β -amino- α -diazoesters (entries 35–38 and 20–21). However, it was found that this aminoalkylation was not efficient with diazomethylenephosphonate derivative (entry 39).

The proposed mechanism for the aminoalkylation reaction of β -amino- α -diazoesters implies initial deprotonation of the amino-group of **1** with sodium hydride to produce anion **A**, which undergoes cyclization to form enolate **B/C** (Scheme 3). The following nucleophilic attack of the enolate at the electrophile which approaches from the less sterically hindered site leads to the formation of the corresponding 1,2,3-triazoline **2** in a highly diastereoselective fashion.

Noteworthy, the β -amino- α -diazooesters **1** are easily available via the previously reported methods proceeding via base-^[11] or acid-mediated^[12] addition of diazoacetates to imines. Furthermore, β -pyridylamino- α -diazooesters can be obtained through a three-component coupling reaction previously developed in our group (Scheme 1).^[7] Accordingly, the newly discovered aminoalkylation reaction opens a direct access to triazolines starting from commercially available aldehydes, amines, diazocompounds, and alkyl halides. To this end, we demonstrated the feasibility of this approach by an efficient gram-scale synthesis of 1,2,3-triazoline **2aa** via a formal four-component coupling reaction of 2-aminopyridine, aldehyde, diazocompound, and benzyl bromide (Scheme 4).

In continuation of our studies on the synthesis of heterocycles via transition metal-catalyzed cycloisomerization reactions of alkynes^[13] and transannulation reactions of triazoles,^[14] a potential heterocyclization reaction of propargyl triazolines **2as-av** was investigated (Scheme 5, eq. 1). Upon screening different transition metal catalysts, it was found that under the Au-catalyzed conditions, propargyl triazolines **2as-av** undergo denitrogenative cycloisomerization reaction with the formation of tetrasubstituted pyrroles **5** (Scheme 5, eq. 1). It is believed that first, triazoline **2** produces enamine **E** through a metal-catalyzed denitrogenative rearrangement of the open triazoline form **D**.^[15] A subsequent aminoauration of the triple bond of **E** results in the formation of a vinyl-gold intermediate **F**.^[16] The latter upon protodemetalation and aromatization gives pyrrole **3**.^[17] The proposed mechanism was supported by observation of trace amounts of intermediate **E** in the reaction mixtures. Moreover, by treatment of triazoline **2aw** with AgBF₄ we were able to isolate enamine **4** in good yield. The latter under the standard Au-catalyzed reaction conditions was efficiently transformed into pyrrole **3c** (Scheme 5, eq. 2).

The reaction works with *N*-pyridyl and *N*-acyl triazolines possessing ethyl- and phenyl substituted propargyl moieties producing pyrroles **3a-d** in good yields. The substrates possessing -Br and -CF₃ substituents at the aryl ring were also capable reactants producing the corresponding pyrroles **3e, f** in moderate yields. This cycloisomerization process represents the first example of denitrogenative transannulation reaction of 1,2,3-triazolines with alkynes, that is complementary to the denitrogenative transannulation of 1,2,3-triazoles.^[14,18]

In conclusion, we developed a highly diastereoselective intramolecular aminoalkylation reaction of β -amino- α -diazooesters leading to the tetrasubstituted 1,2,3-triazolines. The reaction features a novel 1,3-addition of nucleophile and electrophile to the diazo-group of a diazocompound. It proceeds with a variety of C-electrophiles and demonstrates a broad scope with respect to the substituent at the amino- and aryl group of β -amino- α -diazooesters, as well as good functional group tolerance. We also discovered the first gold-catalyzed intramolecular denitrogenative transannulation reaction of propargyl triazolines into pyrroles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Previous works: 1,1-addition of E and Nu to the diazo-group **This work: 1,3-addition of E and Nu to the diazo-group** **Scheme 1.**

Reaction of diazocompounds with nucleophiles and electrophiles: 1,1- and 1,3 addition.

Scheme 2. Diastereoselective aminoalkylation of β -pyridylamino- α -diazoester **1aa**.

Scheme 3.

The proposed mechanism for the aminoalkylation reaction of β -amino- α -diazoesters.

Scheme 4.

Four-component semi-one-pot synthesis of triazoline **2aa** from 2-aminopyridine, aldehyde, ethyl diazoacetate and benzyl bromide. *p*-Tol = 4-CH₃C₆H₄, Py = 2-pyridyl.

Scheme 5.

The Au-catalyzed cycloisomerization of triazolines into pyrroles.

Table 1

The scope of the aminoalkylation reaction of β -amino- α -diazoesters **1**.^[a]

entry	product	yield (%)
1	<p>2ab</p>	71
2	<p>2ac</p>	81
3	<p>2ad</p>	49
4	<p>2ae</p>	58
5	<p>2af</p>	85
6	<p>2ag</p>	36 ^[b]

entry	product	yield (%)
7	<p>1ah'</p>	65
8	<p>1ai'</p>	61 ^[c]
9	<p>2aj</p>	87 64 ^[d]
10	<p>2ak</p>	83
11	<p>2al</p>	91
12	<p>2am</p>	89
13	<p>2an</p>	86

entry	product	yield (%)
14	<p>2ao</p>	69
15	<p>2ap</p>	78
16	<p>2aq</p>	71
17	<p>2ar</p>	75
18	<p>2as, R = Et</p>	69
19	<p>2at, R = Ph</p>	59
20	<p>2au, R = Br</p>	64
21	<p>2av, R = CF₃</p>	58
22	<p>2aw, R = Et</p>	62
23	<p>2ax, R = Ph</p>	76

entry	product	yield (%)
24	<p>2ay</p>	70
25	<p>2az</p>	59
26	<p>2ba</p>	41
27	<p>2bb</p>	45
28	<p>2bc</p>	71 ^[e]
29	<p>2bd</p>	79 ^[e]
30	<p>2be</p>	56 ^[e]

entry	product	yield (%)
31	<p>2bf</p>	47 66[<i>ff</i>]
32	<p>2bg</p>	49[<i>gl</i>]
33	<p>2bh</p>	67
34	<p>2bi</p>	59
35	<p>2bj</p>	70
36	<p>2bk</p>	67
37	<p>2bl</p>	54

entry	product	yield (%)
38	<p>2bm</p>	62
39		[h]

[a] Isolated yields, *d.r.* >99:1 in all cases unless otherwise noted.

[b] *d.r.* 97:3.

[c] NMR yield.

[d] BnOTf was used.

[e] MeI was used.

[f] *n*-BuI was used.

[g] *i*-PrI was used.

[h] Trace of product, the starting diazo compound was recovered.

Py = 2-pyridyl, *p*-Tol = 4-CH₃C₆H₄, *o*-Tol = 2-CH₃C₆H₄, Cbz = carboxybenzyl, Boc = *tert*-butoxycarbonyl.