ORGANIC LETTERS

2009
Vol. 11, No. 23
5482−5485

Highly Efficient Cyanoimidation of Aldehydes

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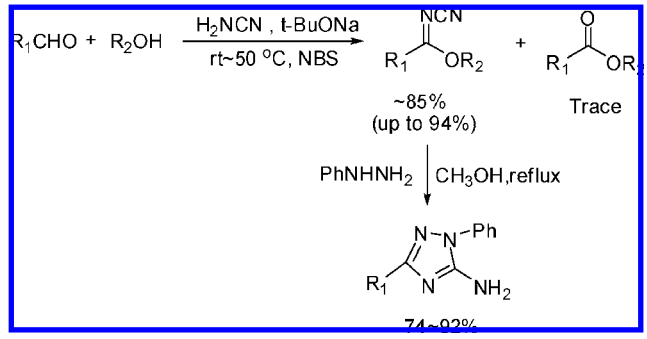
Received October 7, 2009

ABSTRACT



Cyanoimidation of aldehydes using cyanamide as a nitrogen source and using NBS as an oxidant was achieved in high yields without the addition of a catalyst. The method has several advantages, including mild conditions, simple workflow, and inexpensive reagents. The reaction proceeds in a one-pot manner, giving rise to the formation of intermolecular C−N and C−O bonds. Subsequently, the substituted *N*-cyanobenimidate products may also undergo a cyclization reaction to give l,2,4-triazole derivatives in high yields.

The development of efficient and convenient procedures to construct the building blocks of heterocyclic compounds has provoked interest. As such, cyanoimidate derivatives have been widely used as precursors for the synthesis of heterocyclic compounds.[1] *N*-Cyanoimidates can undergo various reactions with a variety of nucleophilic reagents in the construction of N-heterocyclic bioactive compounds, such as hydraziniums, imidamides(amidines), hydroxylamine, amines, and nitriles, all of which were obtained from 3-amino-l,2,4- triazole derivatives, *s*-triazines, 1,2,4-oxadiazoles, isomeric 5-(phenylsulfony1)pyrimidines, and substituted xanthines by application of *N*-cyanoimidates as the key intermediate.[1] Heterocyclic compounds generally possess important biological activities. Many kinds of natural products, pharmaceutical compounds, insecticides, dyes, and solvents are heterocyclic molecules.[2] It is important to synthesize heterocyclic compounds via a convenient route with high yields. Cyanoimidates are attractive chemicals not only because of their unique structure and reactivity but also

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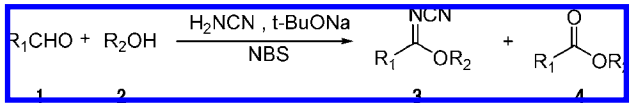
10.1021/ol902207h CCC: $40.75
Published on Web 11/04/2009

because they serve as versatile building blocks for heterocyclic compounds in the fields of organic synthetic chemistry, medicinal chemistry, and materials science. Although cyanoimidates are important chemical reagents, there is a paucity of reliable synthetic methods for producing them.[2] The yields for synthesis of aryl-substituted *N*-cyanoimidates are also unsatisfactory. We report an efficient and convenient synthetic route (Scheme 1) for synthesizing *N*-cyanoimidates via a one-pot reaction of aldehyde derivatives in a *t*-BuONa/NBS system to give aromatic cyanoimidates in good to excellent yields. The results are summarized in Tables 1 and 2.

With an interest in synthesizing potentially bioactive nitrogenous compounds, we focused on the application and prolongation of active nitrogen sources and development of the catalyzed amidation. We found that the saturated C−H bonds of cyclic ethers and tertiary amines could be activated by transition metals.[3] We also attended to a series of studies on metal-catalyzed amidation of aldehydes and amidation of aldehydes under metal-free conditions.[4] Although the methodologies mentioned above were well suited for some amides, such as carboxamide and sulfonamide, and could effectively form carbon−nitrogen bonds, the use of cyanamide as a nitrogen source has never been reported in the literature. As part of our continuing interest in catalyzed amidation, we would like to establish an effective reaction system for the oxidative amidation of aldehydes and ketones

Scheme 1. Cyanoimidation of Aldehydes



using cyanamide as a nitrogen source. In our first attempt to obtain amide derivatives, we chose PhI $(OAc)_2$ as the oxidant and either Al_2O_3 or K_2CO_3 as the base. Unfortunately, products of amidation were not obtained; only the starting material was recovered. However, using *t*-BuOK/NBS with CH_3OH as solvent led to the formation of the nonamidated product *N*-cyanoimidate **3** (Scheme 1).

A possible mechanism for the selective *N*-cyanoimidation−esterification of aldehydes is proposed in Scheme 2. According to route 1, condensation of compound A, which was determined by ^1H NMR and HRMS, occurred at first. The subsequent Michael addition of CH_3OH to *N*-(benzo[*d*][1,3]dioxol-5-ylmethylene) cyanamide generated intermediate B.[5] Subse-

Scheme 2. Tentative Mechanism for Selective Cyanoimidation and Oxidative Esterification of Aldehyde

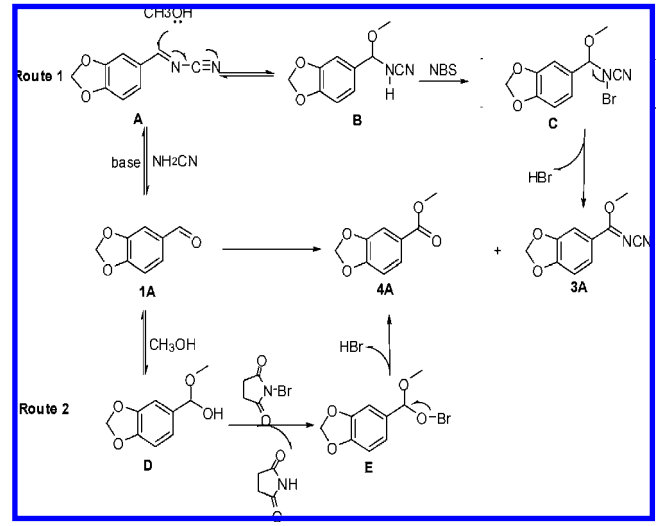
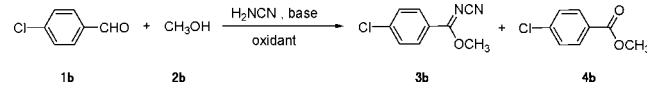


Table 1. Optimization of Selective Reaction Conditions[a]



entry	base	oxidant	% yield (conversion)[b] of **3b**/**4b**
1	*t*-BuONa	SeO_2	trace/−
2	*t*-BuONa	$PhI(OAc)_2$	12/−
3	*t*-BuONa	$CuCl_2$[c]	trace/−
4	*t*-BuONa	NCS	24/−
5	*t*-BuONa	I_2	32/25
6	*t*-BuONa	NBS	64/16
7[d]	*t*-BuONa	NBS	35/37 (86)
8	K_2CO_3	NBS	41/12
9	KOH	NBS	58/15
10[e]	*t*-BuONa	NBS	78/8 (91)
11[f]	*t*-BuONa	NBS	83/trace (94)
12[g]	*t*-BuONa	NBS	85/trace (97)
13		NBS	−/85 (87)

[a] Unless otherwise noted, all reactions were carried out with molar ratio **1b**/H_2NCN/base = 1:1.2:1.5 at rt for 30 min, and then oxidant (1.5 equiv of **1**) was added at 50 °C for 12 h. [b] Isolated yields. [c] 20 mol % catalytic amounts $CuCl_2$ of **1b** were used. [d] The addition of each reagent had no interval. [e] The molar ratio was **1b**/H_2NCN/*t*-BuONa/NBS = 1:2:2:2. [f] The molar ratio was **1b**/H_2NCN/*t*-BuONa/NBS = 1:3:3:3. [g] The molar ratio was **1b**/H_2NCN/*t*-BuONa/NBS = 1:4:4:4.

quently, the active hydrogen of intermediate B was captured by bromine to produce haloamine C in the presence of NBS, finally haloamine C which in the presence of an alkali converted to **3A** with the elimindation of HBr.[6] Similar oxidation and elimination steps were performed via hemiacetal intermediate D and its halide E to generate carboxylic ester **4A** using NBS as an oxidant[7] via route 2.

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Table 2. Cyanoimidation of Aldehydes[a]

entry[a]	R_1	R_2	3	4	% yield (conversion)[b] of 3/4 (conversion)
1	Ph	Me	**3a**	**4a**	87/– (96)
2	p-ClC_6H_4	Me	**3b**	**4b**	85/– (97)
3[c]	p-$CH_3OC_6H_4$	Me	**3c**	**4c**	82/– (57)
4[d]	p-$NO_2C_6H_4$	Me	**3d**	**4d**	67/24 (99)
5	p-BrC_6H_4	Me	**3e**	**4e**	76/16 (96)
6[c]	m-$CH_3OC_6H_4$	Me	**3f**	**4f**	58/– (86)
7[d]	m-$NO_2C_6H_4$	Me	**3g**	**4g**	72/16 (93)
8	m-BrC_6H_4	Me	**3h**	**4h**	94/– (99)
9	m-ClC_6H_4	Me	**3i**	**4i**	83/– (95)
10	1-Naph	Me	**3j**	**4j**	76/– (71)
11	6-quinolyl	Me	**3k**	**4k**	80/– (88)
12	2-thienyl	Me	**3l**	**4l**	49/– (87)
13	Ph	Et	**3m**	**4m**	74/– (98)
14	p-ClC_6H_4	Et	**3n**	**4n**	79/– (90)
15	p-$CH_3OC_6H_4$	Et	**3o**	**4o**	–/–
16[d]	p-$NO_2C_6H_4$	Et	**3p**	**4p**	84/– (99)
17[e]	m-$CH_3OC_6H_4$	Et	**3q**	**4q**	77/– (74)
18[d]	m-$NO_2C_6H_4$	Et	**3r**	**4r**	81/– (96)
19	m-ClC_6H_4	Et	**3s**	**4s**	92/– (87)
20[f]	Ph	i-Pr	**3t**	**4t**	20/– (78)
21	p-$NO_2C_6H_4$	n-Pr	**3u**	**4u**	51/trace (87)
22	o-FC_6H_4	Me	**3v**	**4v**	90/– (99)
23	2,6-di-ClC_6H_3	Me	**3w**	**4w**	84/– (92)
24	o-$CH_3OC_6H_4$	Me	**3x**	**4x**	85/– (98)
25	p-$NO_2C_6H_4$	hydroxyethyl	**3y**	**4y**	–/67 (95)
26	Ph	hydroxyethyl	**3z**	**4z**	–/68 (92)
27[g]	4-formyl C_6H_4	Me	**3I**	**4I**	37/40 (97)
28	4-MeC_6H_4	Me	**3II**	**4II**	72/– (81)
29	n-butyl	Me	**3III**	**4III**	–/–

[a] Unless otherwise noted, all reactions were carried out with molar ratio **1**/H_2NCN/*t*-BuONa = 1:4:4 at room temperature for 30 min. Then NBS (4 equiv of 1) was added at 50 °C for 12 h. [b] Yield of isolated product. [c] The reaction was performed at rt for 6 h. [d] The addition of each reagent had no interval. [e] The reaction temperature was room temperature, and the reaction time was 24 h. [f] The reaction time was 24 h. [g] Product **3I** was methyl-4-((cyanoimino)(methoxy)methyl)benzoate, **4I** was dimethyl *N*,*N*-dicyanoterephthal imidate, and the molar ratio was aldehyde/H_2NCN/*t*-BuONa/NBS = 1:6:6:6.

To evaluate the selectivity of esterification and cyanoimidation, the cyanoimidation reaction of 4-chlorobenzaldehyde was studied by a one-pot reaction to give *N*-cyanoimidate compound **3b** and carboxylic ester compound **4b** with a ratio of 1:1 (Table 1, entry 7). When 4-chlorobenzaldehyde was used as substrate with a substrate/NH_2CN/potassium *tert*-butoxide/NBS molecular ratio of 1:3:3:3, the produced cyanoimidates were obtained with good yield. With the same procedure, several oxidants, such as SeO_2, periodate reagents, such as $PhI(OAc)_2$ and PhI=O, and iodine were tested in CH_3OH in the presence of *t*-BuONa. We validated the general procedure, and the results are shown in Table 1 (entries 1, 2, and 5). It was found that these oxidants and a transition-metal salt (20 mol % of $CuCl_2$) (Table 1, entry 3) resulted in the formation of trace products. Only NBS with the molar ratio (**1b**/H_2NCN/*t*-BuONa/NBS = 1:3:3:3 and **1b**/H_2NCN/*t*-BuONa/NBS = 1:4:4:4) gave high yields of **3b** (Table 1, entries 11 and 12). When using 4-chlorobenzaldehyde as a substrate with **1b**/H_2NCN/*t*-BuONa/NBS in the molecular ratio of 1:1.2:0:1.5, the product methyl 4-chlorobenzoate was obtained with 85% yield, but the formation of cyanoimidate was not observed (Table 1, entry 13). We also examined the effect of bases (Table 1, entries 7–9), which displayed moderate yields of **3b**. On the basis of these results, we used sodium *tert*-butoxide in a molar retio of **1b**/H_2NCN/*t*-BuONa/NBS = 1:3:3:3 and **1b**/H_2NCN/*t*-BuONa/NBS = 1:4:4:4 for subsequenet studies.

To test the universality of the reaction system and the scope of selective cyanoimidation reactions, several different

Scheme 3. Synthesis of 1,2,4-Triazoles

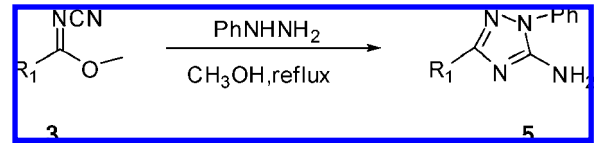
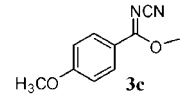
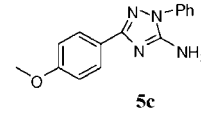
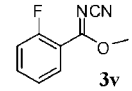
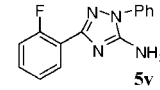
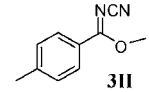
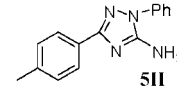
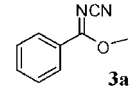
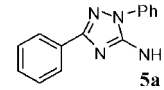
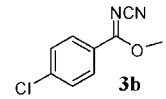
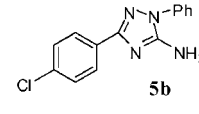
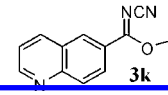
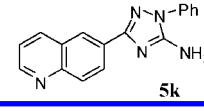


Table 3. Synthesis of 1,2,4-Triazoles[a]

entry	substrate	product	% yield[b]
1	 **3c**	 **5c**	74
2	 **3v**	 **5v**	80
3	 **3ll**	 **5ll**	80
4	 **3a**	 **5a**	92
5	 **3b**	 **5b**	88
6	 **3k**	 **5k**	82

[a] Reactions were performed in CH_3OH in reflux for 4 h with a substrate/$PhNHNH_2$ ratio of 1:1.2. [b] Isolated yields.

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aldehydes were examined. Almost all the substrates could give their corresponding product with good yields (Table 2). However, the yields were moderate or low, and the selectivity could not be ensured when using other alcohols as solvents (Table 2, entries 20, 21, 25, and 26) under identical conditions. A semiselective product **3I** was also obtained with diester **4I** using terephthalaldehyde as the substrate (Table 2, entry 27). In addition, the aliphatic aldehyde could not yield the cyanoimidation product in the reaction system (Table 2, entry 29). From these results, we can conclude that this method could provide a convenient and efficient way for the preparation of substituted *N*-cyanobenimidate from aromatic aldehydes with simple commercially available reagents.

Moreover, methyl *N*-cyanobenzimidate derivatives can undergo a cyclization reaction with hydrazine derivatives to give 1,2,4-triazoles,[8] which can play a key role in pharmacological activity.[9] Thus, we used the products of cyanoimidation of aldehydes to construct nitrogen-containing heterocyclic compounds (Scheme 3). The results demonstrated that several heterocyclic compounds could readily be obtained, all of which are shown in Table 3.

In summary, we have demonstrated an efficient one-pot procedure for the cyanoimidation of aldehydes in the absence of a catalyst to form the corresponding key intermediate *N*-cyanoimidates using NBS as an oxidant. Subsequently, the substituted *N*-cyanobenimidate products were found to be capable of undergoing a cyclization reaction to give l,2,4-triazole derivatives in good yields. The method has several advantages, including mild conditions, simple workflow, high yields, and inexpensive reagents. Further investigation into the pharmacological activity of these heterocyclic compounds is underway and will be reported in due course.

Supporting Information Available: Detailed experimental procedures and characterization data for central compounds are available free of charge via the Internet at http://pubs.acs.org.

OL902207H

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