DOI: 10.1002/ejoc.201001509

Direct Synthesis of Organic Azides from Primary Amines with 2-Azido-1,3-dimethylimidazolinium Hexafluorophosphate

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Keywords: Amines / Azides / Diazo compounds / Heterocycles

Organic azides were prepared from primary amines in high yields by metal-free diazo transfer with 2-azido-1,3-dimethylimidazolinium hexafluorophosphate, which is a stable, crystalline solid that is easy to handle.

Introduction

Organic azides are useful intermediates for the synthesis of nitrogen-containing compounds.[1] The azide group is small and stable under various conditions, but under special conditions it shows characteristic reactivity. For example, organic azides are used as equivalents of primary amines and are employed in the Staudinger reaction.[2,3] Photoinduced nitrene formation of organic azides is widely used for photoaffinity labeling to investigate the identification of the ligand–target receptor and the structure of its binding site.[4,5] Recently, a 1,3-dipole reaction of organic azides and terminal alkynes (Huisgen reaction)[6] revisited center stage in the field of synthetic organic chemistry, as the Cu^{I}-catalyzed reaction was found to be very reliable[7] and was widely used for click chemistry.[8]

Various synthetic methods for organic azides have been developed.[1] Among them, the nucleophilic substitution of organic compounds having a leaving group with an azide ion is a common method (Figure 1). Various alkyl azides are prepared by the reaction of sodium azide and alkyl halides/sulfonates, which are derived from the corresponding alkanols, whereas the synthesis of *tert*-alkyl azides are often not successful because of steric hindrance.[9] Aryl azides are also prepared by substitution, but the generality of the reaction is narrow compared to that of alkyl azides. Aryl halides and aryl diazonium salts are used as electrophiles; the former require a strong electron-withdrawing group at the *para* or *ortho* position to the leaving group, and the latter are limited as substrates because aryl diazonium salts are highly reactive intermediates.

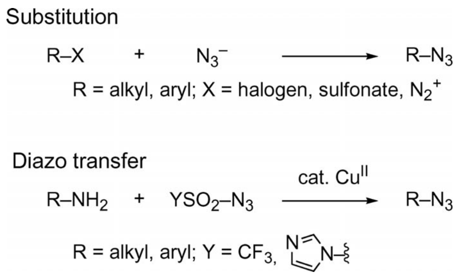

Figure 1. Synthesis of organic azides.

Diazo transfer to primary amines by using trifluoromethanesulfonyl azide (TfN$_3$) by the aid of a Cu^{II} catalyst is an alternative method for the synthesis of organic azides.[10] The process occurs under mild reaction conditions, high yields are obtained for nucleophilic amines, and the transformation requires only one step from the corresponding amines. TfN$_3$, however, has an explosive nature and requires very careful treatment. Lately, imidazole-1-sulfonyl azide hydrochloride has been reported as a diazo transfer reagent; it is crystalline, stable under 80 °C (decomposition temperature), and has almost the same reactivity as TfN$_3$.[11]

Recently, we reported that 2-azido-1,3-dimethylimidazolinium chloride (ADMC, **2**) is an efficient diazo-transfer reagent for 1,3-dicarbonyl compounds (Scheme 1).[12] In this reaction, the diazotized products were easily isolated because the only detectable byproduct, 1,3-dimethyl-2-imidazolidinone (DMI, **4**), was highly soluble in water and was separated from the desired diazo compounds by washing the organic extracts of the reaction mixture with water. Diazo-transfer reagent **2** was prepared from commercially available chloroimidazolinium chloride **1** and sodium azide. Imidazolinium **1** was sensitive to moisture and relatively difficult to handle. Therefore, we expected that if the 2-azido-1,3-dimethylimidazolinium salt was isolated as a stable compound, the reaction using the salt would be performed more conveniently.

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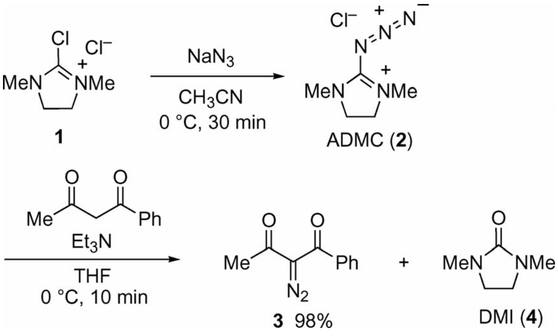
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001509.

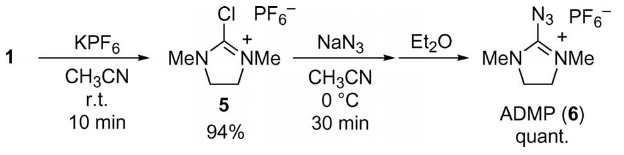


Scheme 1. Diazo transfer of ADMC (**2**) to 1,3-dicarbonyl compound.

However, **2** could not be isolated because of its hygroscopic properties. In contrast, the corresponding hexafluorophosphate salt was isolated as a stable crystalline solid and showed the ability to undergo diazo transfer to primary amines. In this communication, we describe the outcome of this investigation.

Results and Discussion

2-Azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP, **6**) was prepared from **1** as shown in Scheme 2. Following a modified version of Kiso's procedure,[13] anion exchange of **1** was accomplished by treatment of KPF_6 in acetonitrile to afford chloroimidazolinium hexafluorophosphate **5**. The reaction of **5** and sodium azide in acetonitrile and successive reprecipitation by using ether afforded **6** quantitatively. Salt **6** could be stored in a freezer (–10 °C) for at least two months.



Scheme 2. Preparation of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP, **6**).

Both impact sensitivity test[14] and friction sensitivity test[15] showed that salt **6** was negative to explosion in the range of the tests. Figure 2 shows the results of a differential scanning calorimetry (DSC) experiment on **6**. Exothermic decomposition was observed from approximately 200 °C. These results suggest that **6** could be used under its decomposition temperature, preferably under 100 °C with sufficient margin.

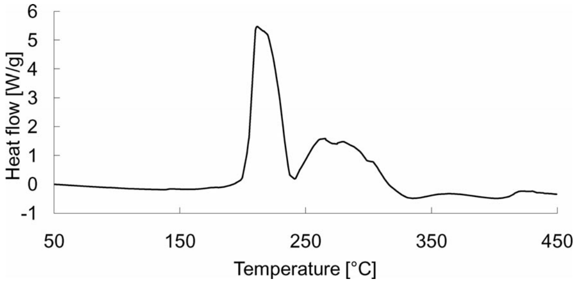
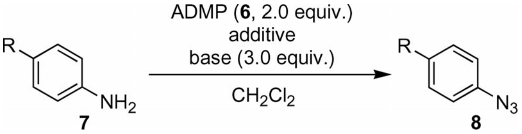


Figure 2. DSC measurement of ADMP (**6**; heating rate: 10 K/min, sample size 3.36 mg, argon atmosphere, open Al pan).

By using **6**, diazo-transfer reactions to primary amines were examined. First the reaction of 4-methoxy aniline with **6** was examined by using Et_3N as a base (Table 1, Run 1). The reaction proceeded smoothly at room temperature to yield *para*-methoxyphenyl azide quantitatively. In this reaction, a detectable byproduct was DMI (**4**), similar to the diazotization of 1,3-dicarbony compounds shown Scheme 2. Compound **4** was easily separated from the desired azide, because their polarities were sufficiently different.

Table 1. Optimization of the diazo transfer of ADMP (**6**) to anilines **7a** and **7b**.



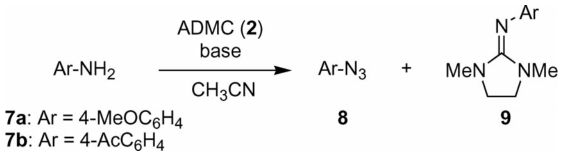
Run	R	7	Base	*T* [°C]	*t* [h]	8	Yield [%][a]
1	MeO	**7a**	Et_3N	r.t.	0.17	**8a**	quant.[b]
2	Ac	**7b**	Et_3N	50	7	**8b**	8
3	Ac	**7b**	DBU	50	7	**8b**	10
4	Ac	**7b**	pyridine	50	7	**8b**	69
5	Ac	**7b**	2,6-lutidine	50	7.5	**8b**	48
6	Ac	**7b**	quinoline	50	6	**8b**	25
7	Ac	**7b**	isoquinoline	50	8	**8b**	64
8	Ac	**7b**	DMAP	50	5	**8b**	83
9[c]	MeO	**7a**	Et_3N	r.t.	0.25	**8a**	quant.[b]
10[c]	Ac	**7b**	DMAP	50	7	**8b**	75

[a] Isolated yield. [b] Determined by ^1H NMR spectroscopy (1,1,2,2-tetrachloroethane was used as an internal standard). [c] The reaction was carried out in the presence of $CuSO_4{\cdot}5H_2O$ (5 mol-%).

Next, *para*-acetylaniline, which is an unsuitable substrate for diazo transfer with TfN_3,[10d] was examined. When Et_3N was used as the base, desired azide **8b** was obtained in only 8%, even though the reaction was carried out at 50 °C for 7 h (Table 1, Run 2). Then the effect of base on this reaction was examined (Table 1, Runs 3–8). Although a strong organic base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was unsuitable for this reaction (Table 1, Run 3), pyridine-type bases were found to be appropriate (Table 1, Runs 4–8). By using *N*,*N*-dimethyl-4-aminopyridine (DMAP), azide **8b** was obtained in 83% yield (Table 1, Run 8). Addition of $CuSO_4$ did not show remarkable effect (Table 1, Runs 9 and 10).

We also examined the reaction of anilines **7a** and **7b** with imidazolinium **2** prepared by the previous report[12] (Table 2). In both cases, the yields of azides **8** were low compared to the results using **6**, and guanidine **9** was also formed. These results suggested that the use of **6** is more efficient for this diazo transfer than the use of an in situ prepared azide imidazolinium salt. The low yield of azide formation may also be attributed to the effect of counteranions, because the yields of **8** using **6** were lower in the presence of Cl^-.[16]

Table 2. Diazo transfer of ADMC (**2**) to anilines **7a** and **7b**.[a]



Run	7	Base	Conditions	Yield [%][b] 8	Yield [%][b] 9
1[c]	**7a**	Et_3N	0 °C, 20 min	48	52
2[d]	**7b**	DMAP	0 °C→reflux, 3.5 h	34	35[d]

[a] To a solution of **2** (prepared by the reaction of **1** and an equimolar amount of NaN_3 in CH_3CN at 0 °C for 30 min.) was added **7** and base. [b] Determined by ^1H NMR spectroscopy for Run 1 (1,1,2,2-tetrachloroethane was used as an internal standard). Isolated yield for Run 2. [c] Ratio **2**/base/**7a** = 1.2:1.2:1. [d] Ratio **2**/base/**7b** = 3:3:1.

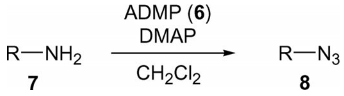
To explore the scope of this reaction, various primary amines were subjected to the diazo-transfer reaction with **6** in the presence of DMAP (Table 3). In Runs 1–13, the results of aromatic amines are shown. Nonsubstituted aniline and anilines having electron-donating groups reacted with **6** smoothly at room temperature to give the corresponding azides in high yields (Table 3, Runs 1–4). By using a slight excess amount of **6** at 50 °C, monohalogen-substituted anilines **7** were transformed into azides in high yields (Table 3, Runs 5 and 6). Even though low nucleophilic anilines substituted with strong electron-withdrawing groups such as acetyl, cyano, and nitro groups were employed, the diazo-transfer reaction proceeded with the use of an excess amount of **6** and DMAP (Table 3, Runs 7–9).

In the case of *ortho*-disubstituted anilines, the effect of substituent is remarkable. Aniline **7j** having dimethyl groups gave the corresponding azide **8j** in good yield, regardless of the steric hindrance, whereas dichloroaniline gave the azide in only 22%, probably due to the low nucleophilicity (Table 3, Runs 10 and 11). 1-Naphthylamines also reacted similarly to the corresponding anilines (Table 3, Runs 12 and 13).

Next, the reaction of ADMP (**6**) with primary alkylamines was examined. In the reaction of 2-phenylethylamine using DMAP, azide **8n** was obtained in only 21% accompanied by the formation of guanidine **9** in 79% (Table 3, Run 14). The yield of azide **8n** increased to 74% when Et_3N was used as the base (Table 3, Run 15). Similarly, Et_3N was better than DMAP as a base in the case of diazotization of cyclohexylamine (Table 3, Runs 16 and 17). The bulkier secondary alkylamines and the tertiary alkylamines were transformed into the corresponding azides in high yields by using DMAP as the base (Table 3, Runs 18–20).

In the diazo-transfer reaction, DMAP showed efficiency as a base, in general, whereas a more nucleophilic base was found to be suitable for highly nucleophilic primary amines.

Table 3. Synthesis of various organic azides **8** from primary amines **7** by using ADMP (**6**).

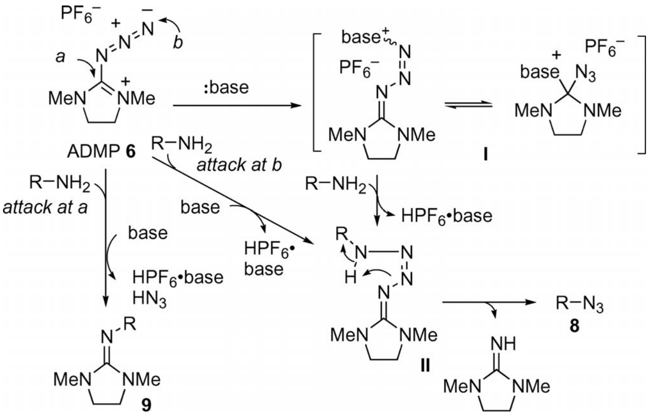


$$\underset{\mathbf{7}}{R{-}NH_2} \xrightarrow[CH_2Cl_2]{\text{ADMP } (\mathbf{6}),\ \text{DMAP}} \underset{\mathbf{8}}{R{-}N_3}$$

Run	R	7	ADMP (6) [equiv.]	DMAP [equiv.]	*T* [°C]	*t* [h]	8	Yield [%][a,b]
1	Ph	**7c**	1.15	1.1	r.t.	2.5	**8c**	87
2	$4\text{-}MeOC_6H_4$	**7a**	1.15	1.1	r.t.	0.5	**8a**	87 (90)
3	$4\text{-}MeC_6H_4$	**7d**	1.15	1.1	r.t.	1.5	**8d**	94
4	4-(*n*Bu)C_6H_4	**7e**	1.15	1.1	r.t.	1.5	**8e**	86 (93)
5	$4\text{-}ClC_6H_4$	**7f**	1.3	1.1	50	3	**8f**	95
6	$4\text{-}BrC_6H_4$	**7g**	1.5	1.1	50	5	**8g**	84 (85)
7	$4\text{-}AcC_6H_4$	**7b**	2	3	50	5	**8b**	83 (15)
8	4-cyano-C_6H_4	**7h**	2	3	50	4	**8h**	63 (7)
9	$4\text{-}O_2NC_6H_4$	**7i**	2	3	50	4	**8i**	61
10	$2,6\text{-}Me_2C_6H_3$	**7j**	1.5	1.1	50	3.5	**8j**	73
11	$2,6\text{-}Cl_2C_6H_3$	**7k**	2	3	50	4	**8k**	22
12	1-naphthyl	**7l**	1.3	1.1	50	1.5	**8l**	92
13	4-nitro-1-naphthyl	**7m**	2.0	3	50	6	**8m**	43
14	$PhCH_2CH_2$	**7n**	1.15	1.1	r.t.	0.25	**8n**	21[c]
15	$PhCH_2CH_2$	**7n**	1.15	5[d]	r.t.	0.25	**8n**	74[e]
16	*c*Hex	**7o**	1.15	1.1	r.t.	0.25	**8o**	31[f,g]
17	*c*Hex	**7o**	1.15	5[d]	r.t.	0.25	**8o**	85[f,h]
18	$Ph(CH_3)CH$	**7p**	1.15	1.1	r.t.	1	**8p**	73, 94[f]
19	Ph_3C	**7q**	1.15	1.1	50	6	**8q**	99
20	1-adamantyl	**7r**	1.15	1.1	r.t.	0.33	**8r**	71

[a] For the comparable reaction with TfN_3, see ref.[10d] Yield in parentheses is that from ref.[10d] [b] Isolated yield. [c] Guanidine **9** was obtained in 79% yield. [d] Et_3N was used instead of DMAP. [e] Guanidine **9** was obtained in 24% yield. [f] Determined by ^1H NMR spectroscopy (1,1,2,2-tetrachloroethane was used as an internal standard). [g] Guanidine **9** was obtained in 49% yield. [h] Guanidine **9** was obtained in 10% yield.

Bases have two roles: the neutralization of the formed acid and the activation of ADMP. On the basis of this consideration, a possible reaction mechanism is depicted in Scheme 3. In the case where the base is more nucleophilic than the primary amine, the base first reacts with **6** to form intermediate **I**, which is substituted with a primary amine to form intermediate **II**, the salt of HPF_6, and base. Intramolecular proton abstraction in **II** occurs to afford corresponding azide **8**. In the case where the primary amine is more nucleophilic than the base, the primary amine attacks at both the *a* and *b* positions in **6** to give guanidine **9** and azide **8**, respectively.



Scheme 3. Plausible reaction mechanism.

Conclusions

We have synthesized 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADMP, **6**), which was isolated as a stable crystalline solid. ADMP shows efficient diazo-transfer ability to primary amines even without the aid of a metal salt such as Cu^{II}. Using this diazotization approach, various alkyl/aryl azides were obtained directly from the corresponding primary amines in high yields and were easily isolated.

Experimental Section

2-Azido-1,3-dimethylimidazolinium Hexafluorophosphate (ADMP, 6): To a solution of chloroimidazolinium hexafluorophosphate (**5**; 2.35 g, 7.8 mmol) in CH_3CN (8 mL) was added sodium azide (717 mg, 11 mmol) at 0 °C, and the mixture was stirred for 30 min. The mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was dissolved in a small amount of CH_3CN (ca 2 mL), and the solution was poured into ether to form a precipitate, which was collected by suction filtration to afford **6** (2.27 g) quantitatively. M.p. 203–205 °C (decomp.). ^1H NMR (400 MHz, CD_3CN): δ = 3.74 (s, 4 H) 3.01 (s, 6 H) ppm. ^{13}C NMR (100 MHz, CD_3CN): δ = 55.0, 33.8 ppm. IR (nujol): $\tilde{\nu}$ = 2360, 2173, 1647, 1578 cm^{-1}. $C_5H_{10}F_6N_5P$ (285.13): calcd. C 21.06, H 3.54, N 24.56; found C 21.07, H 3.42, N 24.27.

Typical Procedure for the Diazo Transfer of ADMP (6) to Primary Amines: ADMP (**6**; 573 mg, 1.15 mmol) in CH_2Cl_2 (2 mL) was added to a solution of 4-aminoacetophenone (**7b**; 136 mg, 1.0 mmol) and *N*,*N*-dimethyl-4-aminopyridine (DMAP; 367 mg, 3.0 mmol) in CH_2Cl_2 (2 mL) at room temperature. The mixture was stirred for 5 h at 50 °C. The reaction was quenched with aq.$NaHCO_3$ (20 mL), and the organic materials were extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were washed with water (30 mL) and brine (30 mL) and then dried with anhydrous sodium sulfate. The solvent was removed in vacuo to afford the crude compound, which was purified by flash column chromatography (silica gel, hexane/ethyl acetate = 9:1) to give **8b** (134 mg, 83% yield; Table 1, Run 8).

Supporting Information (see footnote on the first page of this article): General methods, experimental procedure for the synthesis of **5**, and physical data of **5** and **8**.

Acknowledgments

This work was partially supported by Nagase Science Technology Foundation and a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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[14] Impact sensitivity was >25 Nm by German Federal Institute for Materials Research and Testing (BAM) procedure.

[15] Friction sensitivity was >360 N by German Federal Institute for Materials Research and Testing (BAM) procedure.

[16] In the presence of LiCl, the reaction mixture gradually became complex, as monitored by TLC, and the yields of diazotized products **8** were low. For example, the yield of **8a** became 68% in the presence of LiCl under nearly identical conditions to those outlined in Table 1, Run 1 (Et_3N as the base). In the case of diazo transfer to **7b** with ADMP in the presence of LiCl under nearly identical conditions to those outlined in Table 1, Run 8 (DMAP as the base), the yield of **8b** was 52% after heating at reflux for 5 h.

Received: November 10, 2010