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Direct Synthesis of Acyl Azides from Carboxylic Acids Using 2-Azido-1,3-dimethylimidazolinium Chloride

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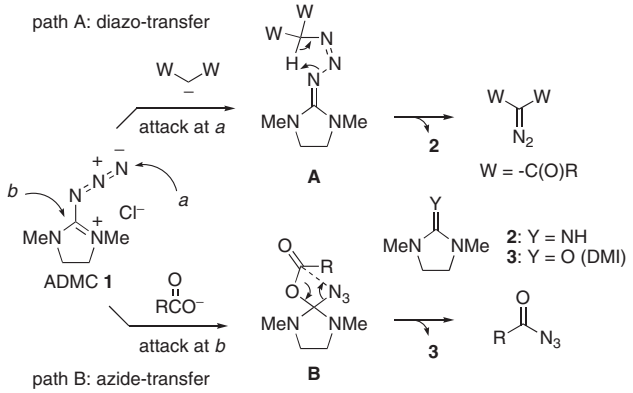
Acyl azides were directly synthesized from carboxylic acids by the treatment with 2-azido-1,3-dimethylimidazolinium chloride (ADMC, **1**) and amine. This procedure resulted in acyl azides in good yields and was applied to the amidation of amino acid derivatives without racemization of the products.

Acyl azides are useful in organic synthesis because of their unique reactivity.[1] For example, the Curtius rearrangement is used as a key reaction for the synthesis of nitrogen-containing compounds such as amides and aza-heterocycles. Furthermore, acyl azides are used as appropriately activated acid derivatives for the synthesis of peptides.

Previously acyl azides were prepared by *N*-nitrosation of acyl hydrazides, while they are now more commonly prepared from the corresponding carboxylic acids by the following two-step sequence: i) transformation of the carboxylic acid to activated acid such as acid chloride or acid anhydride, ii) substitution with an azide ion.[2] To avoid the need for isolation of activated acid, a one-pot procedure has been developed.[2b,3] Direct transformation from carboxylic acids has also been investigated for the synthesis of acyl azides, in which commercially available diphenylphosphoryl azide (DPPA) is commonly used.[4] However, the development of alternate reagents is desired from the viewpoint of atom economy.[5]

Recently, we reported that 2-azido-1,3-dimethylimidazolinium chloride (ADMC, **1**) is an efficient diazo-transfer reagent for 1,3-dicarbonyl compounds (Scheme 1, path A).[6] Nucleophiles attack **1** either at the terminal nitrogen atom (position *a*) or at the carbon position connected to three nitrogen atoms (position *b*). In the diazo-transfer reaction, the products are formed via the intermediate **A**, which is formed by nucleophilic attack at position *a*. We had anticipated that azide transfer would proceed when an oxygen nucleophile such as carboxylate was added to ADMC **1** if the thermodynamic stability of 1,3-dimethyl-2-imidazolidinone (DMI, **3**) is a driving force (path B). In fact, acyl azides were found to be synthesized by the reaction of ADMC **1** and carboxylic acid in the presence of a base. This procedure was subsequently utilized in amide formation. In this letter, we describe the outcome of the investigation.

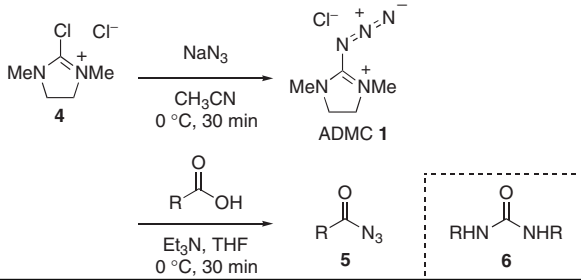


Scheme 1. Diazo/azide-transfer with ADMC **1**.

Acyl azides were synthesized by the reaction of ADMC **1** and carboxylic acid in the presence of Et_3N as shown in Table 1. To a solution of ADMC **1** prepared by the reaction of commercially available chloroimidazolinium salt **4** and sodium azide in acetonitrile at 0 °C for 30 min, a carboxylic acid and triethylamine in THF were added at 0 °C.

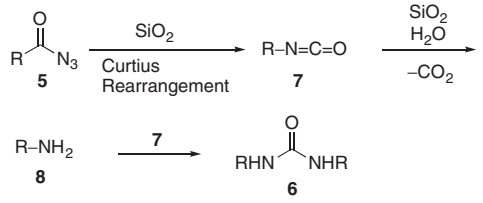
Benzoic acid was quantitatively transformed to the corresponding acyl azide (Run 1). In this reaction, the formation of DMI **3** was observed, which suggested that the reaction proceeded in the expected manner, as shown in Scheme 1. Various aroyl azides could be synthesized at a faster rate in good yields regardless of the substituent on *ortho*-, *meta*-, or *para*-position of the aryl group (Runs 2–9).

Table 1. Synthesis of various acyl azides with ADMC **1**



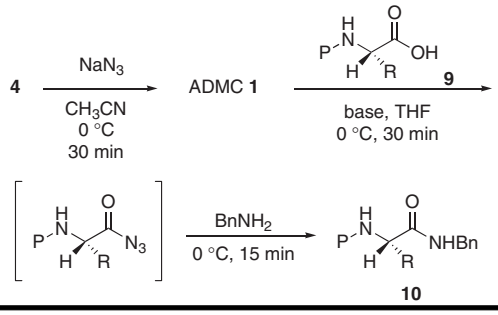
Run	R	Time/h	Yield/%[b]
1	Ph	0.5	100
2	4-MeC_6H_4	0.5	61
3	4-$MeOC_6H_4$	1.5	97
4	4-$NO_2C_6H_4$	3	86
5	3-$MeOC_6H_4$	0.5	95
6	2-MeC_6H_4	0.5	86
7	2-$MeOC_6H_4$	0.5	58
8	2-$NO_2C_6H_4$	1	61
9	2,6-$(MeO)_2C_6H_3$	0.5	41
10	$PhCH_2CH_2$	0.5	48[c] [91][d]
11	Ph_2CH	0.5	30[e]

[a]Molar ratio of **4**/NaN_3/carboxylic acid/Et_3N = 1.2/1.2/1/2. [b]Isolated yield. [c]Urea **6** was isolated in 43% yield. [d]Determined by ^1H NMR of crude compounds. 1,1,2,2-Tetrachloroethane was used as an internal standard. [e]Urea **6** was isolated in 50% yield.



Scheme 2. Formation of urea **6**.

Table 2. Amidation of amino acids with ADMC **1**[a]



Run	**9** P	R	Base	Time /h	**10** Yield[b]/%	ee/%[c]
1	**9a** Cbz	CH_3	Et_3N	4	**10a**	90	>99
2	**9b** Boc	CH_2OBn	*i*-Pr_2NEt	1	**10b**	80	>99

[a]Molar ratio of **4**/NaN_3/**9**/base/$BnNH_2$ = 1.3/1.3/1/2/1.2. [b]Isolated yield. [c]Enantiomeric excess (ee) was determined by HPLC analysis, see Ref. 8.

In the case of aliphatic acids, the corresponding acyl azides were formed, while urea **6** was formed in the isolation step. For example, in the reaction of 3-phenylpropionic acid, acyl azide was detected in 91% yield in the crude product (Run 10). However, pure acyl azide **5** was obtained in only 48% yield after purification using silica gel column chromatography, and urea **6** was obtained in 43% yield. Urea **6** was formed by the reaction of isocyanate **7** formed by the Curtius rearrangement of **5** and amine **8** following hydrolysis of the isocyanate **7** using silica gel, as shown Scheme 2.

Acyl azides are often used as intermediates for synthesizing peptides, and the azide coupling procedure is regarded as a low racemization method.[4,7] The racemization could occur at the stage of acyl azide preparation and/or at the amidation step. We examined the amidation of amino acid derivatives using ADMC **1** (Table 2). First the amidation of Cbz–Ala–OH **9a** and benzylamine was examined (Run 1). To a solution of ADMC **1** in CH_3CN, **9a** was added. After stirring the mixture for 4 h, monitoring consumption of **9a** using TLC, benzyl amine was added to the reaction mixture. After further stirring for 15 min, amide **10a** was obtained in 90% yield without racemization.[8,9] Next, Boc–Ser(OBn)–OH **9b**, which has the highest susceptibility to racemization, was employed for the amidation.[7,10] Although racemization of the product **10b** was observed when Et_3N was used as a base, amide **10b** was obtained as an enantiomerically pure form in 80% yield when *i*-Pr_2NEt was used.[8]

In conclusion, we have developed a new direct synthetic route to acyl azides from carboxylic acids using 2-azido-1,3-dimethylimidazolinium chloride (ADMC, **1**) which surpasses DPPA from the view-point of reagent atom economy. Furthermore, we demonstrated the racemization-free amidation of amino acid derivatives using salt **1**.

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