JOC Notes

Preparation of Polyfunctional Acyl Azides

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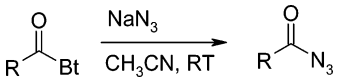


A general synthesis of acyl azides from the corresponding *N*-acyl benzotriazoles is described. The procedure affords acyl azides in good yields and avoids the use of acid activators and NO^+ equivalents typically employed to synthesize these compounds from acid chlorides and hydrazides, respectively.

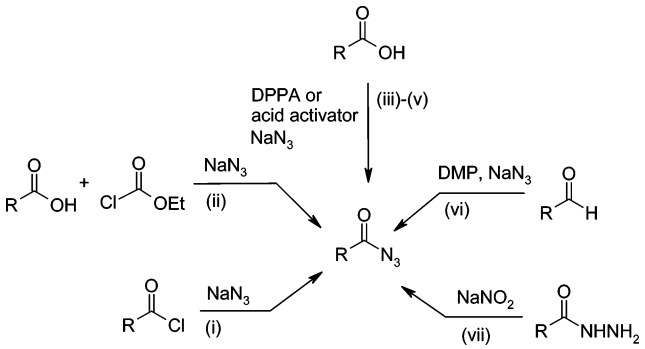
Acyl azides (**1**) have found widespread use as highly reactive reagents in organic chemistry: in cycloadditions, they are used for the preparation of amides by N-acylation and by thermal Curtius rearrangement to isocyanates, which in turn undergo easy conversion into urethanes, ureas, and other derivatives.[1,2]

Acyl azides are commonly prepared (Scheme 1) by reactions

1

of sodium azide with (i) acid chlorides[3−7] or (ii) mixed anhydrides.[8−16] Acid chlorides are not always easy to access or store, and they are highly sensitive to moisture and require care in handling. Mixed anhydrides need to be generated from a carboxylic acid and alkyl chloroformate. We located only a single successful preparation of a Fmoc-protected amino acid azide from the corresponding acid chloride or mixed anhydride.[7] Attempts to prepare acyl azides from the corresponding (*Z*)-α,*β*-unsaturated acids via the mixed anhydride with ethyl chloroformate followed by reaction with sodium azide led to isomerization to (*E*)-α,*β*-unsaturated acyl azides.[12,13]

SCHEME 1. Survey of Literature Syntheses of Acyl Azides



Direct conversion of carboxylic acids to acyl azides is achieved (iii) using diphenylphosphoryl azide (DPPA) in the presence of base (Scheme 1);[6,12,13,17−23] the use of DPPA also reduces *Z*→*E*-isomerization in α,*β*-unsaturated azides.[12] Other suggested protocols for direct conversion of carboxylic acids to acyl azides use (iv) "acid activators" such as $SOCl_2$/DMF[24−27] or cyanuric chloride/*N*-methylmorpholine.[28] (v) Triphosgene/triethylamine[29] also converts various aryl and alkyl carboxylic acids into the corresponding acyl azides (Scheme 1), but this method is not applicable to *N*-Boc-amino acids because of the

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(1) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297 and references therein.
(2) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
(3) van Reijendam, J. W.; Baardman, F. *Synthesis* **1973**, 413.
(4) Erhardt, P. W. *J. Org. Chem.* **1979**, *44*, 883.
(5) Pfister, J. R.; Wymann, W. E. *Synthesis* **1983**, 38.
(6) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595.
(7) Babu, V. V. S.; Ananda, K.; Vasanthakumar, G.-R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4328.
(8) Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511.
(9) Overman, L. E.; Taylor, G. F.; Petty, C. B; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.
(10) Chorev, M.; MacDonald, S. A.; Goodman, M. *J. Org. Chem.* **1984**, *49*, 821.
(11) Kobayashi, S.; Kamiyama, K.; Iimori, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 2557.
(12) Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397.
(13) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735.
(14) Bolm, C.; Dinter, C. L.; Schiffers, I.; Defrère, L. *Synlett* **2001**, 1875.
(15) Kuramochi, K.; Osada, Y.; Kitahara, T. *Tetrahedron* **2003**, *59*, 9447.
(16) Binder, D.; Habison, G.; Noe, C. R. *Synthesis* **1977**, 255.
(17) Shioiri, T.; Ninomiya, K.; Yamada, S.-i. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
(18) Pavia, M. R.; Lobbestael, S. J.; Taylor, C. P.; Hershenson, F. M.; Miskell, D. L. *J. Med. Chem.* **1990**, *33*, 854.
(19) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett.* **1998**, *39*, 7235.
(20) Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4308.
(21) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217.
(22) Kedrowski, B. L. *J. Org. Chem.* **2003**, *68*, 5403.
(23) Holt, J.; Andreassen, T.; Bakke, J. M.; Fiksdahl, A. *J. Heterocycl. Chem.* **2005**, 259.
(24) Arrieta, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 3365.
(25) New, J. S.; Christopher, W. L.; Yevich, J. P.; Butler, R.; Schlemmer, R. F., Jr.; VanderMaelen, C. P.; Cipollina, J. A. *J. Med. Chem.* **1989**, *32*, 1147.
(26) Chambers, J.; Reese, C. B. *Tetrahedron Lett.* **1975**, *32*, 2783.
(27) Padwa, A.; Crawford, K. R.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2003**, *68*, 2609.
(28) Bandgar, B. P.; Pandit, S. S. *Tetrahedron Lett.* **2002**, *43*, 3413.
(29) Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron Lett.* **2002**, *43*, 1345.

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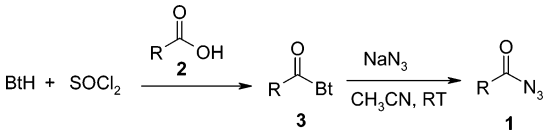
SCHEME 2. Synthesis of Acyl Azides



formation of oxazolidin-2,5-diones (Leuchs' anhydrides).[30] (vi) Dess-Martin periodinane (DMP) and sodium azide have given direct conversion of aldehydes to acyl azides, but the reaction has to be conducted below 0 °C to suppress thermal rearrangement to isocyanate.[31] (vii) Acyl azides can also be prepared from acylhydrazines[32−39] with NO^+ equivalents, but this requires availability of the hydrazide (Scheme 1).

Although methods (i)−(vii) are available for the preparation of acyl azides, the majority involve acid chlorides as intermediates, which are difficult to achieve for many amino- or hydroxy-substituted, unsaturated, heteroaromatic acids or those with other sensitive functionalities. Thus a new and convenient method for the preparation of acyl azides would be advantageous.

Recently, we described the synthesis of a wide range of *N*-acylbenzotriazoles **3** as stable alternatives to acid chlorides,[40,41] which have been used as acylation agents for the preparation of amides,[42−44] Weinreb amides,[45] cinnamoyl hydrazides,[46] *N*-acylsulfonamides,[47] and substituted 2-azinyl-1-ethanones.[48] Herein, we report their application to the preparation of acyl azides.

N-Acylbenzotriazoles **3** are accessible in excellent yields from benzotriazole, thionyl chloride, and the appropriate carboxylic acid **2** according to established procedures.[40,41] Treatment of **3** with sodium azide (1.5 equiv) in acetonitrile at room temperature for 16 h afforded acyl azides in 72−83% yield (Scheme 2 and Table 1). Reaction of sodium azide with chiral *N*-(Cbz-aminoacyl)benzotriazoles provides the corresponding azides without racemization as demonstrated by the L-form and DL-form of phenylalanine. The chirality control in the synthesis was confirmed by comparison of chiral HPLC chromatograms of L-**1l** with DL-**1m**, which showed two peaks for DL-**1m** and one single peak for L-**1l**, which demonstrated chiral preservation in the synthesis of α-amino acyl azides.

TABLE 1. The Preparation of Acyl Azides 1

			Literature		
1	R	yield %[a]	method	ref	yield %
a	C_6H_5	82 (80)	iv	28	86[b]
b	4-$CH_3C_6H_4$	82 (81)	v	29	83[b]
c	2-thienyl	80 (79)	ii	16	73[b]
d	2-furanyl	75 (71)	iv	27	84[b]
			vii	34	22[c]
e	2-indolyl	78 (76)	vii	33	75[c]
f	2-pyridyl	80 (73)	iv	49	34[c]
g	3-pyridyl	78 (72)	iv	28	73[b]
			vii	39	58[c]
h	4-pyridyl	82 (73)	iii	23	80[b]
			iv	18	75[b]
i	PhCH=CH	72 (71)	iv	28	84[b]
			v	29	72[b]
j	2-furanyl−CH=CH	81 (76)	iv	25	83[b]
k	3-hydroxy-2-naphthyl	81 (77)	vii	32	81[c]
l	L-Cbz-Phe	85 (81)	−	−	−
m	DL-Cbz-Phe	88 (82)	−	−	−
n	L-Tryp	83 (77)	−	−	−

[a] Overall yield from acid is in parentheses. [b] Overall yield from acid. [c] Yield from hydrazide.

In conclusion, this approach affords a variety of acyl azides **1a**−**n** in overall good yields that are comparable to the literature for the simple aromatic acid azides (**1a**, **1b**) but improved for compounds **1c**,**e**−**g** under mild conditions. The procedure avoids the following: (1) the use of cyanuric chloride, triphosgene, and diphenylphosphoryl azide (DPPA) as reagents; (2) the use of hydrazides and NO^+ equivalents in multistep reactions for **1d**,**e**,**s**,**k**; (3) isomerization of α,β-unsaturated derivatives; (4) racemization of the chiral center when amino acid derivatives were used; and (5) Curtius rearrangements.

Experimental Section

Typical Procedure for Preparation of Acyl Azides 1a−n: Sodium azide (1.5 mmol, 97 mg) was added to a solution of appropriate *N*-acylbenzotriazoles (1 mmol) in acetonitrile (10 mL). One drop of water was added, and the mixture was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was dissolved in diethyl ether and washed with dilute aqueous sodium carbonate and water. The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography using hexane/diethyl ether (2:1) to give the acyl azides **1a**−**n**.

***N*-Benzyloxycarbonyl-L-phenylalanine Azide (1l):** yield 85%; white microcrystals (Et_2O/hexane); mp 148−149 °C; $[\alpha]^{23}_D$ = −2.90° (*c* 1.39, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79−2.87 (m, 1H), 3.04−3.10 (m, 1H), 4.15−4.22 (m, 1H), 5.00 (s, 2H), 7.19−7.36 (m, 10H), 7.66 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.5, 55.6, 65.3, 126.4, 127.5, 127.8, 128.2, 128.3, 129.1, 137.0, 128.0, 156.0, 173.4. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.96; H, 4.98; N, 17.28. Found: C, 63.28; H, 5.16; N, 16.88.

***N*-Benzyloxycarbonyl-DL-phenylalanine Azide (1m):** yield 88%; white microcrystals (Et_2O/hexane); mp 130−132 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79−2.86 (m, 1H), 3.04−3.10 (m, 1H), 4.15−4.22 (m, 1H), 5.00 (s, 2H), 7.19−7.36 (m, 10H), 7.67 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.5, 55.6, 65.3, 126.4, 127.6, 127.8, 128.2, 128.3, 129.1, 137.0, 138.0, 156.0, 173.4. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.96; H, 4.98; N, 17.28. Found: C, 63.24; H, 5.17; N, 16.89.

(30) Wilder, R.; Mobashery, S. *J. Org. Chem.* **1992**, *57*, 2755.
(31) Bose, D. S; Reddy, A. V. N. *Tetrahedron Lett.* **2003**, 3543.
(32) Wolf, G.; Friedman, O. M.; Dickinson, S. J.; Seligman, A. M. *J. Am. Chem. Soc.* **1950**, *72*, 390.
(33) Rinderknecht, H.; Koechlin, H.; Niemann, C. *J. Org. Chem.* **1953**, *18*, 971.
(34) Yale, H. L.; Losee, K.; Martins, J.; Holsing, M.; Perry, F. M.; Bernstein, J. *J. Am. Chem. Soc.* **1953**, *75*, 1933.
(35) Saxena, S.; Haksar, C. N. *Curr. Sci.* **1979**, *48*, 63.
(36) Nettekoven, M. *Synlett* **2001**, 1917.
(37) Tarabara, I. N.; Yarovoi, M. Y.; Kas'yan, L. I. *Russ. J. Org. Chem.* **2003**, *39*, 1676.
(38) Macor, J. E.; Mullen, G.; Verhoest, P.; Sampognaro, A.; Shepardson, B.; Mack, R. A. *J. Org. Chem.* **2004**, *69*, 6493.
(39) Papeo, G.; Posteri, H.; Vianello, P.; Varasi, M. *Synthesis* **2004**, 2886.
(40) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Synthesis* **2003**, 2795.
(41) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656.
(42) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
(43) Katritzky, A. R.; Yang, B.; Semenzin, D. *J. Org. Chem.* **1997**, *62*, 726.
(44) Katritzky, A. R.; Wang, M.; Yang, H.; Zhang, S.; Akhmedov, N. G. *ARKIVOC* **2002**, *viii*, 134.
(45) Katritzky, A. R.; Yang, H.; Zhang, S.; Wang, M. *ARKIVOC* **2002**, *xi*, 39.
(46) Katritzky, A. R.; Wang, M.; Zhang, S. *ARKIVOC* **2001**, *ix*, 19.
(47) Katritzky, A. R.; Hoffmann, S.; Suzuki, K. *ARKIVOC* **2004**, *xii*, 14.
(48) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Akhmedova, R. G. *ARKIVOC* **2005**, *vi*, 329.
(49) Saikachi, H.; Kitagawa, T.; Nasu, A.; Sasaki, H. *Chem. Pharm. Bull.* **1981**, *29*, 237.

***N*-Benzyloxycarbonyl-L-tryptophane Azide (1n):** yield 83%; white microcrystals (Et_2O/hexane); mp 166−168 °C; $[\alpha]^{23}_D$ = −8.76° (*c* 1.39, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.79−3.06 (m, 1H), 3.18−3.24 (m, 1H), 4.23−4.30 (m, 1H), 4.99 (q, J = 12.7 Hz, 2H), 7.00 (t, J = 7.2 Hz, 1H), 7.07−7.11 (m, 1H), 7.19 (s, 1H), 7.31−7.38 (m, 6H), 7.56 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 10.88 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.0, 55.0, 65.4, 110.2, 111.5, 118.2, 118.5, 121.0, 123.9, 127.2, 127.7, 127.8, 128.4, 136.2, 137.1, 156.1, 173.9. Anal. Calcd for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.72; N, 19.27. Found: C, 63.12; H, 5.04; N, 19.52.

Supporting Information Available: Experimental procedures, spectroscopic data, and melting points for compounds **1a**−**k**, and copies of the ^{1}H and ^{13}C NMR spectra of compounds **11**−**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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