Together with the known substitutions of the resulting sulfonyl tetrazoles, the two-step sequence is formally equivalent to regioselective cycloadditions of azides with a wide variety of nitriles. Further studies on the scope of this chemistry will be reported.[20]

Experimental Section

Note: Many low-molecular-weight azides are known to be explosive. In this lab, no problems have been encountered, but great caution should be exercised when heating compounds of this type, especially neat. The reactions described here were run on only a few grams; an increase in the scale of these reactions will decrease the efficiency of heat dissipation and explosions may result.

A vial was charged with a stir bar, *p*-toluenesulfonyl cyanide (905 mg, 5.0 mmol), and azide (5.0 mmol), and tightly capped. The reagents were stirred neat in an oil bath set to 80 °C, for 16 h. If the reaction was not complete at this time, stirring was continued, in some cases with the temperature reset to 100 °C. In the cases of unhindered azides, the crude product, a light yellow solid, was analytically pure. To remove color, the product can be dissolved in a mixture of ethyl acetate (30 %) and hexanes (70 %), and run down a short plug of silica gel to yield a white solid. If excess toluenesulfonyl cyanide was present, the product was crushed and placed under vacuum at 80 °C for four hours. In the case of hindered azides, the product was purified by column chromatography, by eluting with ethyl acetate (10 %) and hexanes (90 %), to give the product as a white or light-tan solid. In some cases (**9**, **14**) the product was sufficiently insoluble that trituration with ethyl acetate (10 %) and hexanes (90 %) was sufficient to purify the compound.

Received: February 11, 2002 [Z 18692]

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[1] R. N. Butler in *Comprehensive Heterocyclic Chemistry*, *Vol. 4* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, UK, **1996**.

[2] a) V. A. Ostrovskii, M. S. Pevzner, T. P. Kofmna, M. B. Shcherbinin, I. V. Tselinskii, *Targets Heterocycl. Syst.* **1999**, *3*, 467 – 526; b) M. Hiskey, D. E. Chavez, D. L. Naud, S. F. Son, H. L. Berghout, C. A. Bome, *Proc. Int. Pyrotech. Semin.* **2000**, *27*, 3 – 14.

[3] H. Singh, A. S. Chawla, V. K. Kapoor, D. Paul, R. K. Malhotra, *Prog. Med. Chem.* **1980**, *17*, 151 – 183.

[4] a) R. Huisgen, J. Sauer, H. J. Sturm, J. H. Markgraf, *Chem. Ber.* **1960**, *93*, 2106; b) D. Moderhack, *J. Prakt. Chem.* **1988**, *340*, 687 – 709.

[5] a) A. Michael, *J. Prakt. Chem.* **1893**, *48*, 94; b) R. Huisgen, *Proc. Chem. Soc.* **1961**, 357 – 369; c) R. Huisgen, *Angew. Chem.* **1968**, *80*, 329 – 337; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 321 – 328.

[6] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056 – 2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004 – 2021.

[7] W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radic, P. R. Carlier, P. Taylor, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 1095 – 1098; *Angew. Chem. Int. Ed.* **2002**, *41*, 1053 – 1057.

[8] a) The Chemistry of the Cyano Group (Ed.: Z. Rappaport), New York, Interscience, **1970**, p. 351; some recent examples: b) Z. P. Demko, K. B. Sharpless, *Org. Lett.* **2001**, *3*, 4091 – 4094; c) B. Davis, T. Brandstetter, C. Smith, L. Hackett, B. G. Winchester, G. Fleet, *Tetrahedron Lett.* **1995**, *36*, 7507 – 7510; d) D. Korakas, A. Kimbaris, G. Varvounis, *Tetrahedron* **1996**, *52*, 10 751 – 10 760; e) T. C. Porter, R. K. Smalley, M. Teguiche, B. Purwono, *Synthesis* **1997**, *7*, 773 – 777.

[9] a) W. G. Finnegan, R. A. Henry, R. Lofquist, *J. Am. Chem. Soc.* **1958**, *80*, 3908 – 3911; b) S. J. Wittenberger, *Org. Prep. Proced. Int.* **1994**, *26*, 499 – 531; c) Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945 – 7950.

[10] H. Quast, L. Bieber, *Tetrahedron Lett.* **1976**, *18*, 1485 – 1486.

[11] W. R. Carpenter, *J. Org. Chem.* **1962**, *27*, 2085 – 2088.

[12] M. M. Krayushin, A. M. Beskopylnyi, S. G. Zlotin, O. A. Lukyanov, V. M. Zhulin, *Izv. Akad. Nauk. SSSR Ser. Khim.* **1980**, *11*, 2668.

[13] These 1-substituted-5-sulfonyl tetrazole systems are known, and the most common route for their synthesis is by the addition of sodium azide or trimethylsilyl azide to an isothiocyanate, to give the tetrazole thiol (see references [13a, 13b]), followed by alkylation (see reference [13c]), and oxidation to the sulfone (see reference [13d]). A less common route to such 1-substituted,5-mercaptotetrazoles is by metalation of a 1-alkylated, 5*H*-tetrazole with *n*-butyl lithium, followed by reaction with elemental sulfur (see reference [13e]). Direct alkylation of 1*H*,5-sulfidotetrazoles provides no control of regiochemistry (see references [1] and [4f]). a) E. Lieber, J. Ramachandran, *Can. J. Chem.* **1959**, *37*, 101 – 109; b) E. Lieber, R. Slutkin, *J. Org. Chem.* **1962**, *27*, 2214 – 2217; c) H. Alper, R. W. Stout, *J. Heterocycl. Chem.* **1973**, *10*, 5 – 10; d) K. Ishii, H. Hatanak, I. Ueda, *Chem. Pharm. Bull.* **1991**, *39*, 3331 – 3334; e) R. Rapp, *Can. J. Chem.* **1971**, *49*, 2139 – 2142; f) R. A. Henry, *J. Heterocycl. Chem.* **1976**, *13*, 391 – 392.

[14] a) A. M. van Leusen, A. J. W. Iedema, J. Strating, *J. Chem. Soc. Chem. Commun.* **1968**, 440 – 441; b) J. M. Cox, R. Ghosh, *Tetrahedron Lett.* **1969**, *39*, 3351 – 3352.

[15] a) R. D. Allan, B. Twitchin, *Aust. J. Chem.* **1980**, *33*, 599 – 604; b) P. Byard, F. Sainte, R. Beaudegnies, L. Ghosez, *Tetrahedron Lett.* **1988**, *29*, 3799 – 3802.

[16] a) J. Goerdeler, H. W. Linden, H, Puff, R. Hundt, *Chem. Ber.* **1985**, *118*, 3241 – 3247; b) H. Gotthardt, J. Blum, *Chem. Ber.* **1986**, *119*, 1445 – 1454.

[17] J. March, *Advanced Organic Chemistry*, Wiley, New York, **1992**, chap. 13, pp. 641 – 676.

[18] a) M. A. Goltsberg, G. I. Koldobskii, *Russ. J. Org. Chem.* **1995**, *31*, 1552 – 1553; b) M. A. Goltsberg, G. I. Koldobskii, *Russ. J. Org. Chem.* **1996**, *32*, 1194 – 1201; c) M. A. Goltsberg, G. I. Koldobskii, *Chem. Heterocycl. Comp.* **1996**, *32*, 1300 – 1304; d) A. P. Koreneva, G. I. Koldobskii, *Russ. J. Org. Chem.* **2000**, *36*(11), 1698 – 1699.

[19] Regioselectivities observed are from 3:1 to 9:1 with propiolates (references a, b). Recent work in our laboratory (V. Rostovsev et al., unpublished results) as well as in reference c has shown that copper acetylides add to azides with complete regioselectivity; a) D. Clarke, R. W. Mares, H. J. McNab, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1799 – 1804; b) K. Hirota, H. Hosono, Y. Kitade, Y. Maki, C. K. Chu, R. F. Schinazi, H. Nakane, K. Ono, *Chem. Pharm. Bull.* **1990**, *39*, 2597 – 2601; c) C. W. Torne, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*(9), 3057 – 3064.

[20] Note added in proof: We have recently become aware of a patent which describes the [2 + 3] cycloaddition of a number of sulfonyl cyanides and azides. Only one yield is given, and the yield and procedure are not as efficient as described here; see D. H. Klaubert, J. H. Sellstedt, US Pat. 4,526,978, July 2, **1985**.

A Click Chemistry Approach to Tetrazoles by Huisgen 1,3-Dipolar Cycloaddition: Synthesis of 5-Acyltetrazoles from Azides and Acyl Cyanides[**]

Zachary P. Demko and K. Barry Sharpless[*]

Dedicated to Professor Rolf Huisgen

The preceding communication[1] describes the facile [2+3] cycloaddition of azides and *p*-toluenesulfonyl cyanide to form 5-sulfonyl tetrazoles, interesting compounds in their

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[**] We thank the National Institute of General Medical Sciences, National Institutes of Health (GM-28384), the National Science Foundation (CHE-9985553), the Skaggs Institute for Chemical Biology for a Predoctoral Fellowship (Z.D.), and the W. M. Keck Foundation for financial support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

own right, and made all the more so by the ease of nucleophilic substitution of the 5-sulfonyl group. Just being a highly convergent route to useful tetrazoles makes this cycloaddition an interesting transformation, but its real value becomes apparent after examining the experimental details for the reaction: solvent-free fusion of the reactants at 80–100 °C affords the pure product in essentially quantitative yield.

Herein, we expand this methodology to include acyltetrazoles, which are similarly arranged for rapid functionalization. As in the preceding report, the yields are very high, and isolation is simple. In addition, as both azides and acyl cyanides are readily accessible, a modular approach to the synthesis of tetrazoles is possible—all in keeping with the tenets of "click chemistry".[2] Together with its complementary Huisgen 1,3-dipolar-cycloaddition route to triazoles ($RN_3 + RC{\equiv}CR$),[3] which, in the case of propiolates and copper acetylides, gives predominantly the 1,4-isomer,[4] these reactions provide a direct route to the various substituent patterns around an azole-ring system (Scheme 1).

It has been demonstrated that increasing the electron-withdrawing strength of the substituent bound to a nitrile tends to increase its rate of cycloaddition to azides.[5] Sulfonyl and perfluoroalkyl groups are among the most electron-withdrawing uncharged groups commonly encountered in chemistry,[6] thus it is not surprising that nitriles bound to these groups readily participate in this [2+3] cycloaddition.[1, 7] Are there other electron-poor nitriles which are activated enough to take part in the formation of synthetically useful tetrazoles?

Two obvious choices, fluorinated aromatic nitriles and heteroaromatic nitriles, did not react with azides when heated, nor did some other unusual heteroatom-bound nitriles, such as dialkyl cyanophosphates. Carbonyl cyanides, while not as electron poor as sulfonyl cyanides, nor as hydrolytically stable, have the advantage of being readily available.[8] It has been demonstrated that certain acyl cyanides undergo a [2+3] cycloaddition with organic azides at a pressure of 10 kbar,[9] and also that ethyl cyanoformate undergoes a [2+3] reaction with certain organic azides upon heating,[10] both in moderate yield. We were pleased to find that a broad range of acyl cyanides,[11] cyanoformates,[12] and cyanoformamides[13] undergo a regioselective [2+3] cycloaddition with azides upon heating, neat, at 120–130 °C and ambient pressure, to give 1-substituted-5-acyl-tetrazoles in high yield (see Scheme 1, left).

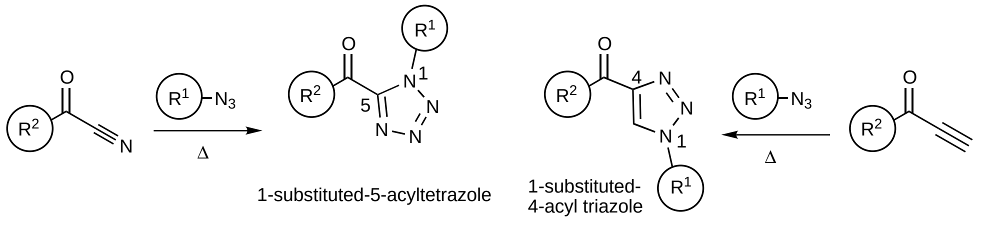
To our knowledge, this report describes the first example of the direct synthesis of 1-substituted-5-acyltetrazoles[14] by an intermolecular [2+3] cycloaddition between an organic azide and an acyl cyanide at ambient pressure. Moreover, when aroyl cyanides or alkanoyl cyanides with no α proton are used in conjunction with unhindered azides as the substrate, the yields are above 90 %, and the purification is very simple, as it involves only a liquid–liquid extraction and a filtration—clearly a good "click" reaction. As dozens of acyl cyanides are commercially available, and countless more are available in one step from acyl halides, great diversity can be rapidly accessed with this cycloaddition. In addition, further important synthetic transformations are immediately available through the active aryl-ketone moiety, oxime, and hydrazone derivatives, for example.[15]

The scope of viable azide substrates is quite broad. Primary azides, when heated neat with benzoyl cyanide, provide products in 94–98 % yields (see Table 1, compounds **1**–**6**). Purification is also very simple—stirring the crude reaction mixture with aqueous potassium carbonate in a two-phase system for an hour hydrolyzes all of the unreacted acyl cyanide and, after passing the organic layer through a short plug of silica, evaporation yields the pure product. More hindered azides also react cleanly with benzoyl cyanide, although the yields are lower (**7** and **8**). When aryl azides are used as substrates, only decomposition is observed.

The scope of the reaction with various acyl cyanides is also quite broad, provided that there is not a proton in the α position (see Table 2). Aroyl cyanides react cleanly with benzyl azide to give the corresponding tetrazoles (**9**–**11**); furoyl cyanide is also a good substrate, although the reaction is not as clean (**12**). Pivaloyl cyanide is an excellent substrate (**13**), however, alkanoyl cyanides with a proton at the α position, for example pyruvoyl cyanide, show largely decomposition upon prolonged heating (**14**). This decomposition is presumably because of loss of HCN, to form the highly reactive ketene. Cyanoformamides and cyanoformates are also competent substrates (**15** and **16**). When unsaturated acyl cyanides are used as substrates, for example cinnamoyl cyanide, only decomposition is observed, even when no α proton was present, such as in α-methyl cinnamoyl cyanide.

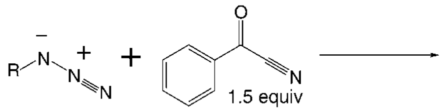
A search for a more versatile route to acyltetrazole derivatives, one which would enable post-cycloaddition modification, lead to 4-nitrophenyl cyanoformate (**17**). When **17** is heated neat with benzyl azide at 120 °C, the corresponding activated tetrazole **18**, is produced in excellent yield. As a nitrophenolate ester of an electron-deficient heterocyclic carboxylic acid, **18** can be easily derivatized by nucleophiles (Scheme 2). As nitrophenyl esters are unstable to moisture, isolation by chromatography or crystallization gives poor yields. Fortunately, when the tetrazole formation and nucleophilic displacement reactions are run in one pot, the yields of the corresponding acyltetrazoles are generally high.

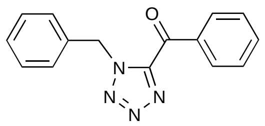
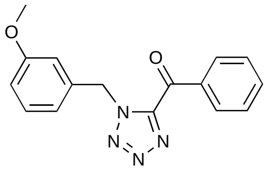
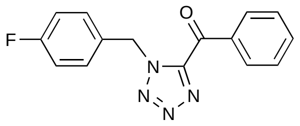
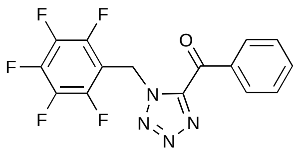
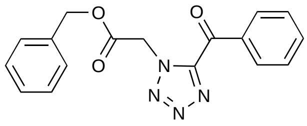
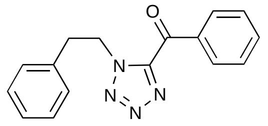
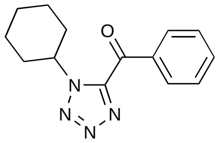
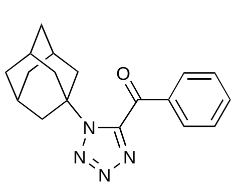
The use of **17** allows one to bring together an azide and a nucleophile in one pot to form, in high yield, a 1-substituted-5-acyltetrazole (see Scheme 3). This highly con-



Scheme 1. Direct [2+3] cycloaddition routes to disubstituted acyltetrazoles and triazoles.

Table 1. Reaction of azides and benzoyl cyanide.[a]

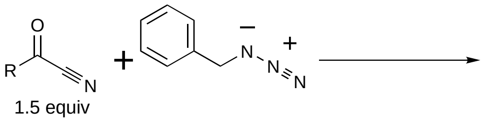


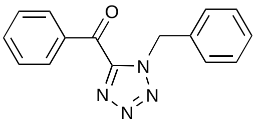
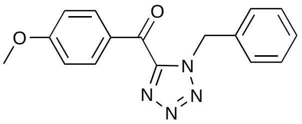
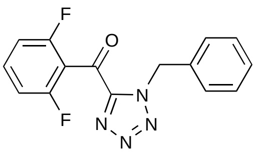
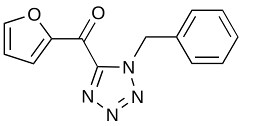
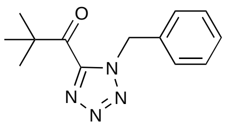
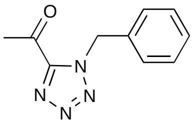
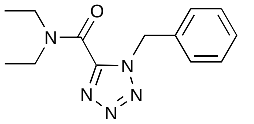
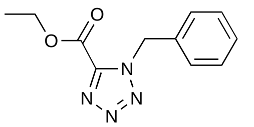
Compound	Product	Time [h]	Yield [%]
1		60	98
2		40	94
3		60	95
4		40	94
5		60	96
6		60	96
7		40	85
8[b]		80	75

[a] Reaction conditions: 1) neat, 120 °C, 2) stir with 10 % Na_2CO_3, 3) filter through silica pad. [b] Product was collected by filtration and trituration.

vergent route elegantly complements the triazole cycloaddition chemistry mentioned in the introduction, as carbonyl-substituted acetylene derivatives are known to react with azides to give 1,4-disubstituted triazoles with relatively good regioselectivity (see Scheme 1). These two reactions, taken together, provide a "click" route to the various geometries of disubstituted acylazoles.

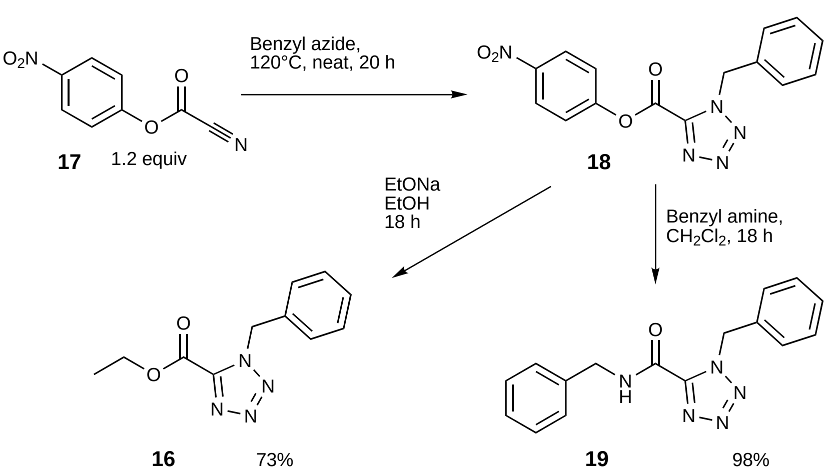
Table 2. Reaction of acyl cyanides with benzyl azide[a].



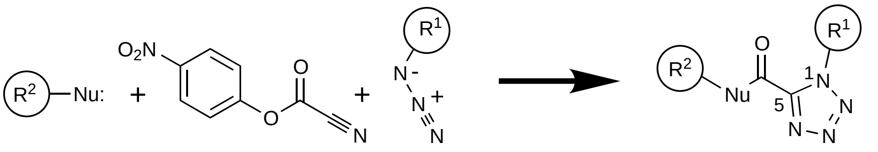
Compound	Product	Time [h]	Yield [%]
9		40	98
10		40	97
11		40	99
12[b]		20	91
13[c]		60	92
14[b,d]		24	62
15[b,c]		60	85
16[b]		40	83

[a] Reaction conditions: 1) neat, 120 °C, 2) stir with 10 % Na^2CO_3, 3) filter through silica pad. [b] Purification by column chromatography was necessary. [b] Reaction run at 130 °C. [d] 10 equivalents of acyl cyanide

In summary, outlined here is a simple route to 1-substituted-5-acyltetrazoles by a [2+3] cycloaddition of readily available acyl cyanides and aliphatic azides. The reactions are high yielding and product isolation is simple. In addition, we found that *p*-nitrophenyl cyanoformate undergoes the same cycloaddition process in high yield, and that the resulting activated esters of the 1-alkyltetrazole-5-carboxylic acid can be captured in situ by nucleophiles such as amines and alkoxides.



Scheme 2. Use of *p*-nitrophenyl cyanoformate as an easily derivatizable acylnitrile source, en route to disubstituted acyltetrazoles.



Scheme 3. A general route to 1-substituted-5-acyltetrazoles.

Experimental Section

Note: Many low-molecular-weight azides, and certain tetrazoles and nitroaromatic compounds, are known to be explosive. In this lab no problems have been encountered, but great caution should be exercised when heating compounds of this type, especially neat. The reactions described here were run on only a few grams; an increase in the scale of these reactions will decrease the efficiency of heat dissipation and explosions could result.

General synthesis of acyltetrazoles: A vial was charged with a stir bar, azide (5.0 mmol), and acyl cyanide (7.5 mmol), and tightly capped. The reagents were stirred in an oil bath set to 120 °C, neat, for 40 h. If the reaction was not complete at this time, it was continued, in some cases with an increase in temperature to 130 °C, until the reaction was complete. The reaction mixture was then cooled, and dissolved in ethyl acetate (10 mL) and added to an aqueous solution of sodium carbonate (10 % w/w, 50 mL) and stirred for one hour. In some cases, longer stirring times and the addition of acetone (20 mL) were necessary to effect the full hydrolysis of the acyl cyanide. The organic layer was isolated and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were diluted with hexanes (60 mL) and run through a short plug of silica gel. The silica plug was washed with an equal amount and composition of solvent. The solvent was evaporated to yield the product.

Received: February 11, 2002 [Z18693]

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[1] Z. P. Demko, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *114*, 2214–2217; *Angew. Chem. Int. Ed.* **2002**, *41*, 2110–2113.

[2] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

[3] a) A. Michael, *J. Prakt. Chem.* **1893**, *48*, 94; b) R. Huisgen, *Proc. Chem. Soc.* **1961**, 357–369; c) R. Huisgen, *Angew. Chem.* **1968**, *80*, 329–337; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 321–328; .

[4] Regioselectivities observed are between 3:1 and 9:1. For precedents, see a) D. Clarke, R. W. Mares, H. J. McNab, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1799–1804; b) K. Hirota, H. Hosono, Y. Kitade, Y. Maki, C. K. Chu, R. F. Schinazi, H. Nakane, K. Ono, *Chem. Pharm. Bull.* **1990**, *39*, 2597–2601.

[5] Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945–7950.

[6] J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, p. 18.

[7] W. R. Carpenter, *J. Org. Chem.* **1962**, *27*, 2085–2088.

[8] S. Hünig, R. Schaller, *Angew. Chem.* **1982**, *94*, 1; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 36–49.

[9] I. V. Zavarzin, V. M. Zhulin, V. N. Yarovenko, M. M. Krayushkin, *Izv. Akad. Nauk SSSR Ser. Khim.* **1988**, *5*, 1168–1170.

[10] a) D. H. Klaubert, J. H. Sellstedt, C. J. Guinosso, S. C. Bell, R. J. Capetola, *Med. Chem.* **1981**, *24*, 748–752; b) D. H. Klaubert, S. C. Bell, T. W. Pattison, *J. Heterocycl. Chem.* **1985**, *22*, 333–336.

[11] a) T. S. Oakwood, C. A. Weisgerber, *Org. Synth. Coll. Vol. 3* **1955**, 112–114; b) N. Sperber, R. Fricano, *J. Am. Chem. Soc.* **1950**, *72*, 2792–2793; c) M. Tanaka, T. Kobayashi, T. Sakakura, *Angew. Chem.* **1968**, *96*, 519–520; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 518–519; d) S. Murahashi, T. Naota, N. Nakajima, *Tetrahedron Lett.* **1985**, *26*, 925–928; e) S. Murahashi, T. Naota, *Synthesis* **1993**, 433–440; f) H. M. R. Hoffmann, K. Haase, Z. M. Ismail, S. Preftitsi, A. Weber, *Chem. Ber.* **1982**, *115*, 3880–3885; g) K. E. Koenig, W. P. Weber, *Tetrahedron Lett.* **1974**, *26*, 2275–2278.

[12] T. V. John, G. L. Larson, C. Subramaniam, US Patent 5,852,207 **1998**.

[13] H. Kobler, K.-H. Schuster, G. Simchen, *Liebigs Ann. Chem.* **1978**, 1946–1962.

[14] These 1-substituted-5-acyltetrazole systems are known, and a variety of routes have been described in the literature, the most common being oxidation of a hydroxymethyl tetrazole (see references [14a, 14b]) or treatment of a 5-alkylated-1-lithiotetrazole with a Weinreb amide (see references [14c, 14d]). Direct alkylation of an acyltetrazole provides poor regioselectivity (see references [14e, 14f]): a) D. Moderhack, A. Beissner, *Z. Naturforsch. B* **1996**, *51*, 1815–1817; b) D. L. Boger, H. Sato, A. E. Lerner, M. P. Hedrick, R. A. Fecik, H. Miyauchi, G. D. Wilkie, B. J. Austin, M. P. Patricelli, B. F. Cravatt, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 5044–5049; c) Y. Satoh, N. Marcopulos, *Tetrahedron Lett.* **1995**, *36*, 1759–1762; d) Y. Satoh, J. Moliterni, *Synlett* **1998**, *5*, 528–530; e) R. E. Ford, P. Knowles, E. Lunt, S. M. Marshall, A. J. Penrose, C. A. Ramsden, A. J. H. Summers, J. L. Walker, D. E. Wright, *J. Med. Chem.* **1986**, *29*, 538–549; f) M. Casey, C. J. Moody, C. W. Rees, R. G. Young, *J. Chem. Soc. Perkin Trans. 1* **1985**, *4*, 741–745.

[15] D. Moderhack, A. Beissner, *Z. Naturforsch. B* **1996**, *51*, 1815–1817.