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Cyano(ethoxycarbonothioylthio)methyl Benzoate: A Novel One-Carbon Radical Equivalent

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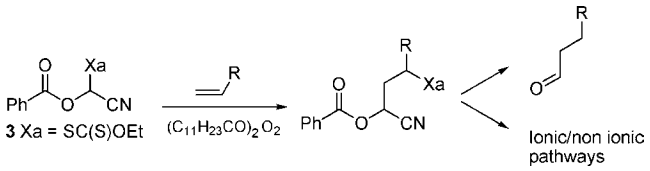
ABSTRACT



Cyano(ethoxycarbonothioylthio)methyl benzoate 3 has been prepared and shown to be an excellent one-carbon radical equivalent that can be applied for the introduction of an acyl unit via xanthate transfer radical addition to olefins. The corresponding adducts can be further elaborated. A rare 1,5-nitrile translocation was also observed during the study.

The generation of acyl radical equivalents and their subsequent intra- or, less frequently, intermolecular addition to a suitably substituted olefin has drawn increasing interest over the past decade.[1] The most commonly encountered form of such acyl radical equivalents is usually based upon a dithioacetal (dithiolane, dithiane),[2] although oxathianes,[2c] acetals,[3] and *N*-alkyl-*N*-phenylamides[4] have shown utility in this capacity. As part of our ongoing research into novel one-carbon radical equivalents, we have recently described the synthetic scope, in this context, of 1,3-dithiane and 1,3-dithiane 1-oxide radicals generated from the corresponding xanthates.[5] The former radicals only underwent detectable addition to significantly electron deficient olefins, thereby reflecting the electron-rich nature of the dative stabilized radical center. By contrast, 1,3-dithiane 1-oxide radicals demonstrated smooth addition to a variety of olefins in the xanthate transfer reaction. This drastic change in reactivity was most likely due to the nature of the radical center being modified from a dative to a synergic captodative stabilized system having enhanced electrophilic character.[6] However, the synthetic scope of 1,3-dithiane 1-oxide radicals was limited by the corresponding xanthate precursor containing two nonfixed stereocenters, which led to complex product mixtures. In addition, the generation of the formyl group required a two-step protocol. Thus, we now report the synthesis and utility of cyano(ethoxycarbonothioylthio) methyl benzoate **3** as a new one-carbon radical equivalent that takes advantage of the captodative effect while having minimal stereochemical complexity, and which allows facile unmasking of the key formyl function through basic hydrolysis. This would parallel the use of protected cyanohydrins as acyl anion equivalents introduced by Stork many years ago.[7]

The preparation of xanthate **3** commenced with the efficient alkylation of benzoic acid with chloroacetonitrile to afford benzoyloxyacetonitrile **1**, followed by NBS mediated bromination to generate the corresponding bromide **2** as a mixture with **1** in a 4.5:1 ratio, respectively (Scheme 1). Treatment of the crude product mixture with potassium *O*-ethylxanthate then cleanly furnished the desired xanthate **3** in an overall yield of 42%.

Notwithstanding the relatively long and incomplete bromination process (22 h, **2**:**1** = 4.5:1) it is nonetheless

(1) For a review of acyl radical chemistry see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(2) (a) Foulard, G.; Brigaud, T.; Portella, C. *J. Org. Chem.* **1997**, *62*, 9107. (b) Byers, J. H.; Whitehead, C. C.; Duff, M. E. *Tetrahedron Lett.* **1996**, *37*, 2743. (c) Nishida, A.; Kawahara, N.; Nishida, M.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 9713. (d) Herrera, A. J.; Studer, A. *Synthesis* **2005**, *9*, 1389.

(3) Stien, D.; Crich, D.; Bertrand, M. P. *Tetrahedron* **1998**, *54*, 10779.

(4) McDonald, C. E.; Galka, A. M.; Green, A. I.; Keane, J. M.; Kowalchick, J. E.; Micklitsch, C. M.; Wisnoski, D. D. *Tetrahedron Lett.* **2001**, *42*, 163.

(5) de Greef, M.; Zard, S. Z. *Tetrahedron* **2004**, *60*, 7781.

(6) Janousek, Z.; Merenyi, R.; Viehe, H. G. *Acc. Chem. Res.* **1985**, *18*, 148.

(7) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1974**, *96*, 5272.

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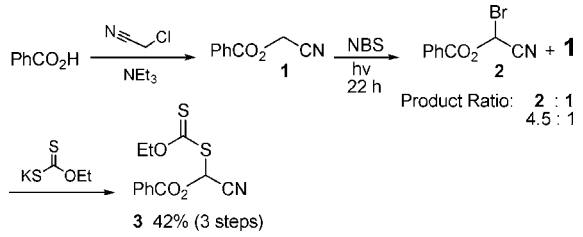
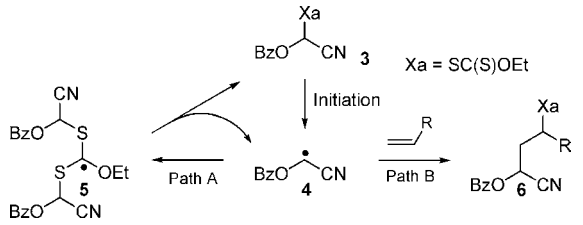
Scheme 1. Synthesis of Xanthate **3**



significant that xanthate **3** can be prepared from cheap and readily available reagents, on a multigram scale, through a short 3-step reaction sequence and in reproducible yield. Moreover, **3** can be stored for many months under an inert atmosphere without detectable decomposition.

With xanthate **3** in hand, we next investigated its ability to undergo group transfer radical addition to olefins. The mechanistic reasoning upon which this work hinges is outlined in Scheme 2.[8] Acyl radical equivalent **4**, generated

Scheme 2. Addition of Acyl Radical Equivalent **4** to Olefins



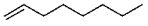
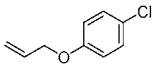
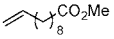
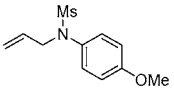
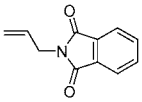
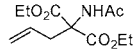
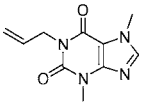
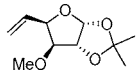
by chemical initiation with lauroyl peroxide (DLP), can be captured by the olefin to produce an intermediate that reacts with the starting material **3** in a dithiocarbonate group transfer propagation step to finally afford a new xanthate adduct **6** (i.e., path B). One important advantage of this system is that the reaction of captodative radical **4** with its xanthate precursor **3** (i.e., path A) is degenerate. Without this major competing pathway radical **4** acquires a relatively long effective lifetime and should be able to undergo efficient addition to even unactivated olefin traps.

In practice, we were pleased to observe that xanthate **3** furnished good to excellent yields of adducts **6a**−**m** when treated with a substoichiometric amount of DLP (5−27%) and the corresponding olefin **a**−**m** (2 equiv) in refluxing 1,2-dichloroethane (DCE) (Table 1).

To investigate the limitations of the xanthate transfer reaction a significant range of olefins were screened. Simple hydrocarbons (entries 1−4) posed no difficulty with excellent conversion being obtained in each instance. The product derived from (−)-*β*-pinene **6c** (entry 3) is particularly interesting since it is formed after initial radical **4** addition followed by fragmentation of the cyclobutane ring to generate a tertiary radical to which the xanthate is transferred (Scheme 3). This is the only case for which adduct **6** does not have

(8) (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, 153−154, 137.

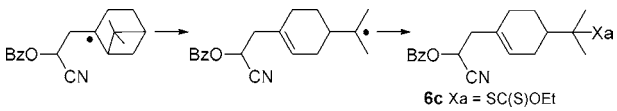
Table 1. Radical Addition of Xanthate **3** to Olefins **a**−**m**[a]

entry		olefin **a-m**	**6a-m** yield (%)[b]	diastereomeric ratio[c]
1	**a**		93	1.1:1
2	**b**		85	1.2:1
3	**c**[d]		90	1.1:1
4	**d**		86	1.3:1.3:1:1
5	**e**		84	1.1:1
6	**f**		65	1.2:1
7	**g**		69	1.1:1
8	**h**		89	1.1:1
9	**i**		88	1.2:1
10	**j**		65	1.2:1
11	**k**		57[e]	1.2:1
12	**l**		79	1.1:1
13	**m**		79	2.2:2.2:1:1

[a] Addition reactions were performed by portionwise addition of DLP (5%) every 90 min to a refluxing degassed 1 M solution of **3** (1 equiv) in DCE in the presence of the olefin (2 equiv) until **3** was completely consumed. [b] Yields are of isolated products. [c] Diastereomeric ratio was measured by NMR spectroscopy after purification by column chromatography. [d] (−)-*β*-Pinene was utilized. [e] The isolated yield is moderate due to a tedious purification of adduct **6k** from olefin **k**.

an identical structure with the generic provided in Scheme 2. Functionality that is widely used in organic synthesis including ethers, acetals (entries 5 and 6), esters (entries 7 and 8), sulfonamides, amides, *N*,*O*-protected amino acids (entries 9−11), together with complex heterocycles and sugars[9] (entries 12 and 13), may also be tolerated. All adducts

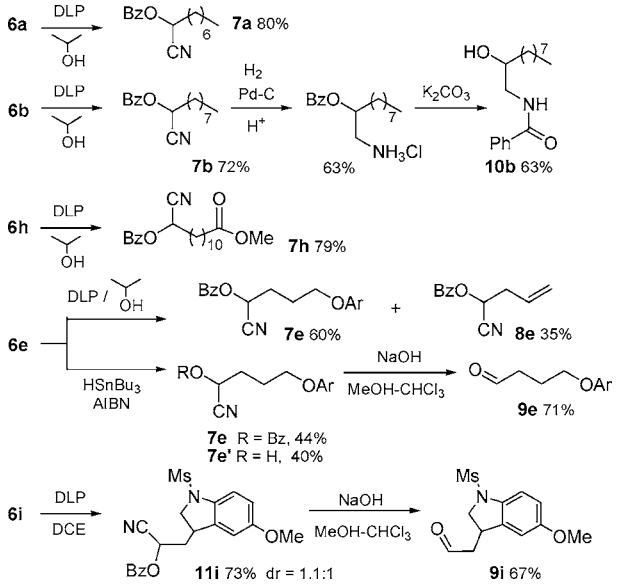
Scheme 3. Formation of Adduct **6c**



6a−**m** were isolated as a mixture of two or more diastereomers (depending on the stereochemical complexity of the olefin employed), with low diastereoselectivity being observed overall. It is noteworthy that since **6a**−**m** still incorporate a xanthate moiety, a variety of further transformations via radical and nonradical processes is possible.[10]

The newly introduced formyl group can be unmasked by initial removal of the xanthate moiety through reduction with a combination of DLP/2-propanol or tributyltin hydride/AIBN, followed by hydrolysis (Scheme 4). The isolated

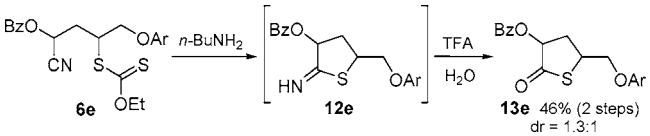
Scheme 4. Reduction of a Selection of Adducts **6a**−**m**



yields of reduced material **7** with use of DLP/2-propanol were greater than via the tinhydride method (72−80% compared with 40−51%), possibly due to tin-mediated cleavage of the benzoate group. Interestingly, the reduction of **6e** to **7e** via the DLP/2-propanol approach resulted in modest C−O bond β-scission of the corresponding radical. Further reduction to *N*-protected amino alcohols is possible (e.g., **7b** to **10b**) via catalytic hydrogenation under acidic conditions (10% Pd−C, HCl−MeOH) followed by base (K_2CO_3) induced migration of the benzoyl moiety.[11,12] The new formyl group can then be obtained from benzoyloxyacetonitrile by mild hydrolysis (NaOH, MeOH−$CHCl_3$), using general procedures described in the literature.[13] As an alternative to reduction, the xanthate group can be used to effect an annulation reaction onto a suitably placed aromatic ring, as in the efficient conversion of adduct **6i** to indoline aldehyde **9i** via the isolated indoline **11i**.[10]

In an attempt to hydrolyze the xanthate group, adduct **6e** was treated with *n*-butylamine at room temperature (Scheme 5). The corresponding thiol was not isolated with the major

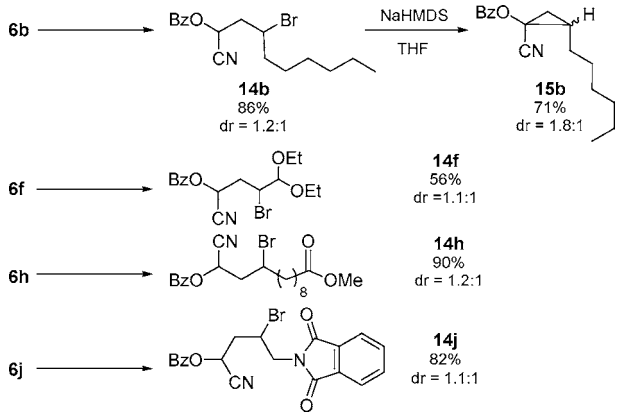
Scheme 5. Cyclization of Adduct **6e**



product being a dihydrothiophen-2-imine **12e**. Imine **12e** was most likely generated through nucleophilic attack of *n*-butylamine onto the xanthate moiety followed by *5-exo-dig* cyclization of the sulfide anion formed onto the pendant nitrile.[14] Subsequent treatment of **12e** with aqueous TFA afforded the corresponding dihydrothiophen-2-one **13e** in good overall yield.[12]

Transformation of the xanthate group in adducts **6** into a bromide can be effected with ease by treatment with ethyl-2-bromo-2-methylpropionate and cumyl peroxide in refluxing dichlorobenzene (Scheme 6).[10e] The corresponding bromides

Scheme 6. Xanthate−Bromine Exchange of Adducts **6**



14 were produced in good to excellent yield and as a mixture of diastereomers in an approximate 1:1 ratio. Initial studies have shown that upon treatment with base, the bromides **14** can be used as precursors to cyclopropanes (e.g., **14b** to **15b**).[12]

With a one-carbon radical equivalent in hand, we briefly explored the possibility of its application to the construction of the α-kainic acid skeleton. α-Kainic acid **16** has attracted considerable interest since it was first isolated in 1953,[15] due to its anthelmintic and neuroexcitory properties.[16,17] It was postulated that xanthate **3** could be utilized to install the C3-carboxyl and C4-*exo*-methylene functionalities in a total

(9) 5,6-Dideoxy-1,2-*O*-isopropylidiene-3-*O*-methyl-α-D-xylo-hex-5-enofuranose was utilized in this case: Josan, J. F.; Eastwood, F. W. *Carbohydr. Res*. **1968**, *7*, 161.

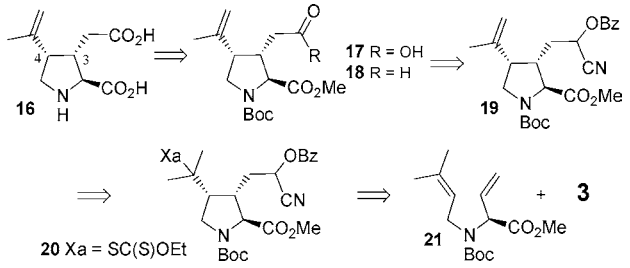
(10) For example, see: (a) Lopez-Ruiz, H.; Zard, S. Z. *Chem. Commun.* **2001**, *24*, 2618. (b) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719. (c) Liard, A.; Quiclet- Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759. (d) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7295. (e) Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Zard, S. Z. *Synlett* **2002**, *5*, 811.

(11) Oaksmith, J. M.; Peters, U.; Ganem, B. *J. Am. Chem. Soc*. **2004**, *126*, 13606.

(12) The reported reaction yields are unoptimized.

(13) (a) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1983**, *66*, 1865. (b) Reymond, J.-L.; Vogel, P. *Tetrahedron*: *Asymmetry* **1990**, *10*, 729. (c) Allemann, S.; Vogel, P. *Synthesis* **1991**, *11*, 923. (d) Konno, S.; Ohba, S.; Sagi, M.; Yamanaka, H. *Heterocycles* **1986**, *24*, 1243. (e) Connors, R.; Durst, T. *Tetrahedron Lett.* **1992**, *33*, 7277. (f) Stierle, D. B.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4980.

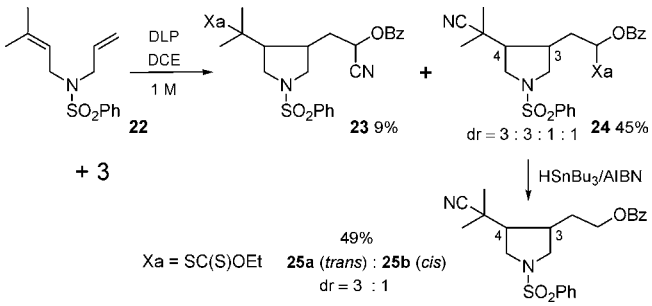
Scheme 7. Retrosynthetic Analysis for Kainic Acid **16**



synthesis of kainic acid (Scheme 7). Radical addition of **3** to diene **21**, followed by ring closure and xanthate transfer would afford the pivotal pyrrolidine **20**. Thermal xanthate elimination to generate olefin **19**, hydrolysis of the benzoyloxyacetonitrile group to give aldehyde **18**, and subsequent oxidation and deprotection would then culminate in the preparation of **16** through a rapid 5-step reaction sequence.

The key radical addition and cyclization step was initially investigated with model diene **22** (prepared by phenylsulfonation and alkylation of allylamine). Thus, treatment of a refluxing 1 M solution of xanthate **3** and diene **22** in DCE with a substoichiometric amount of DLP generated two cyclized adducts **23** and **24** that were constitutional isomers (Scheme 8). To our surprise, what we believe (by NMR and

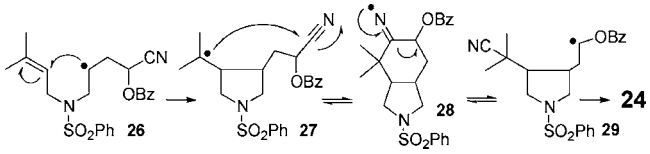
Scheme 8. Model Studies toward Synthesis of **16**



HRMS analysis) to be the expected product **23** was the minor component (9%) while the major product **24** (45%) was a pyrrolidine derived from a rare 1,5-nitrile translocation. Both adducts were isolated as a mixture of four diastereomers after purification by column chromatography.[12,18] The structure of **24** was confirmed by tributyltin hydride/AIBN mediated xanthate reduction, which afforded heterocycle **25** in reasonable yield and as a mixture of two separable diastereomers in a **25a**:**25b** 3:1 ratio.[19] The major diastereomer exhibits a trans relationship between the C3 and C4 substituents based upon NOESY analysis. Dilution of the reaction mixture from 1 to 0.5 M offered no improvement on the isolated yields of **23** and **24** and did not alter the observed diastereomeric ratio.[19]

A number of groups have recently reported 1,4 and 1,5 nitrile translocation reactions in radical processes although the latter mode is far less commonplace.[20] It is likely that the mechanism for formation of **24** from **3** and **22** is similar to that originally proposed by Kalvoda (Scheme 9).[21] Thus, the initially formed radical **26** is subject to *5-exo-trig* cyclization to generate heterocyclic radical **27**, which subsequently cyclizes onto the nitrile to form bicyclic iminyl radical **28**.[14] In the absence of a hydrogen atom source, **28** is prone to β-scission to give radical **29**. Xanthate transfer in the usual fashion (Scheme 2) finally affords the isolated product **24**.

Scheme 9. Postulated Mechanism for Formation of **24**



The diastereoselective formation of a *trans*-C3−C4 junction could result from steric repulsion between the trisubstituted olefin and the benzoyloxyacetonitrile group in **26**, which disfavors cyclization to the cis product. Moreover, cleavage of the C−C═N• bond in **28** is likely to be facilitated by the neighboring phenylester moiety through a combination of bond weakening and stabilization of the ensuing radical **29**.[20e]

In conclusion, xanthate **3** has been demonstrated as a useful alternative to known radical and ionic methods for the introduction of formyl units. It is reactive toward a variety of unactivated olefins, with the corresponding adducts being obtained in excellent yields. Furthermore, it can be introduced under mild reaction conditions and unmasked to furnish a variety of structural units.

Supporting Information Available: Experimental procedures and NMR data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052634M

(14) (a) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Thomas, R. C.; Kruse, L.; Silberman, L. *J. Chem. Soc., Chem. Commun.* **1976**, *18*, 734−741.

(15) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.

(16) (a) Watase, H.; Tomiie Y.; Nitta, I. *Nature* **1958**, *181*, 761. (b) McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven Press: New York, 1978. (c) Shinozaki, H. In *Excitatory Amino Acid Receptors. Design of Agonists and Antagonists*; Krogsgaard-Larsen, P., Hansen, J. J., Eds.; Ellis Horwood: New York, 1992.

(17) For reviews on the syntheses of kainoids, see: (a) Hashimoto, K.; Shirahama, H. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 212. (b) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. For total synthesis of α-kainic acid using radical cyclization, see: (c) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1990**, *46*, 7263. (d) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, *2*, 125. (e) Hannessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (f) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896. (g) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Aoe, K.; Hiramatsu, H.; Naito, T. *Heterocycles* **1997**, *46*, 321. (h) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron* **1999**, *55*, 6153. (i) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199.

(18) Adduct **23** was isolated as a mixture of four diastereomers. However, the low yield of **23** does not permit an accurate diastereomeric ratio to be stated within experimental error.

(19) The diastereomeric ratio **25a**:**25b** 3:1 was determined after purification by column chromatography.

(20) (a) For rates of radical addition to nitriles see: Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* **1979**, *57*, 831. For examples of nitrile translocations see: (b) Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2175. (c) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565. (d) Rychnovsky, S. D.; Swenson, S. S. *Tetrahedron* **1997**, *53*, 16489. (e) Bowman, W. R.; Bridge, C. F.; Brookes, P. *Tetrahedron Lett.* **2000**, *41*, 8989. (f) Callier, A.-C.; Quiclet- Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 6109.

(21) (a) Kalvoda, J. *Helv. Chim. Acta* **1968**, *51*, 267. (b) Kalvoda, J. *Chem. Commun.* **1970**, *16*, 1002.