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Thiomaleic Anhydride: A Convenient Building Block for the Synthesis of α-Substituted γ- and δ-Lactones through Free-Radical Addition, Nucleophilic Ring Opening, and Subsequent Thiocarboxylate Manipulation

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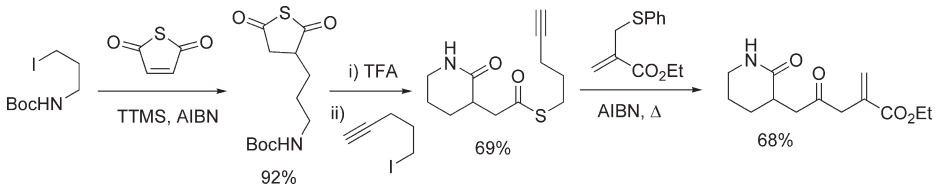

Iodoalkyl *tert*-butyl carbonates and carbamates undergo clean free-radical addition to thiomaleic anhydride to give substituted thiosuccinic anhydrides in high yield on treatment with tris(trimethylsilyl)silane and a radical initiator. After removal of the *tert*-butyloxycarbonyl group, cyclization then affords lactones or lactams substituted in the α-position by a thiocarboxylic acid residue. This group is converted to amides through reaction with electron-deficient sulfonamides or to aldehydes and/or ketones by the reaction of derived thioesters with either thiophenol, an electron-deficient allyl phenyl sulfide, or phenylboronic acid.

Introduction

Monothiomaleic anhydride is an excellent trap for nucleophilic alkyl radicals, capturing, for example, the cyclohexyl radical some 285 times more rapidly than diethyl maleate at 20 °C in dichloromethane solution as determined by Giese and Kretzschmar using the alkylmercury hydride method.[1,2] We conceived that this efficient radical reaction, which has yet to be applied in a preparative sense, would provide a useful extension to the multicomponent coupling processes we have been developing in our laboratory based on the nucleophilic ring-openings of cyclic monothioanhydrides[3] and the powerful chemistry of the ensuing thioacids.[4] In parallel, and to further increase the level of molecular diversity[5] available through this chemistry, we also extend here the chemistry of the intermediate thioacids beyond the amide bond-forming reactions we have previously demonstrated to encompass a variety of C−C bond-forming protcols, both radical and nonradical in nature.

(1) Giese, B.; Kretzschmar, G. *Chem. Ber*. **1982**, *115*, 2012–2014.
(2) For comparison, the cyclohexyl radical adds to maleic anhydride with a relative rate constant with respect to diethyl maleate of 295 under the same conditions.[1]
(3) (a) Crich, D.; Bowers, A. A. *Org. Lett*. **2007**, *9*, 5323–5325. (b) Crich, D.; Sasaki, K.; Rahaman, Md. Y.; Bowers, A. A. *J. Org. Chem*. **2009**, *74*, 3886–3893.
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Results and Discussion

Six *tert*-butoxycarbamyl or *tert*-butoxycarbonyloxy alkyl iodides were prepared from the corresponding amino alcohols and diols by a process involving introduction of a Boc group and subsequent reaction with triphenylphosphine and iodine as described in the Supporting Information.[6]

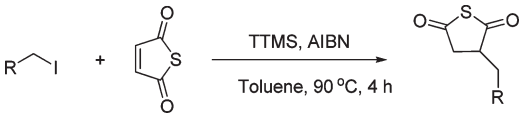
Radical addition reactions were conducted with tris(trimethylsilyl)silane (TTMS)[7] as hydrogen atom donor and chain propagator with azobisisobutyronitrile (AIBN) in toluene at 90 °C, resulting in each case in excellent yields of the adducts after chromatographic purification (Table 1). Somewhat expectedly, in the case of the iodoalanine radical precursor the addition product was formed as a 1:1 mixture of stereoisomers, for which no attempt at separation was made.

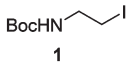
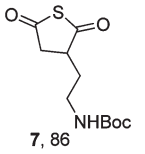
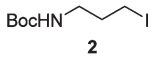
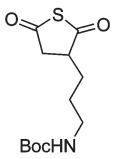
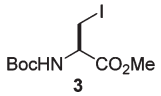
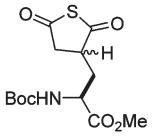
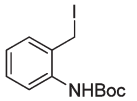
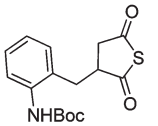
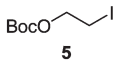
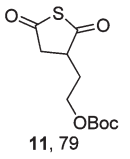
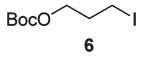
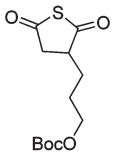
Treatment of the radical adducts with trifluoroacetic acid to release the Boc protecting system was followed by exposure to 2,4,6-collidine resulting in cyclization and generation of the thiocarboxylates in situ. Finally, addition of cesium carbonate and a 2,4-dinitrobenzenesulfonamide[3,4n−p] capped the sequence by amide bond formation (Table 2). In each case, the cyclization step took place to give the more kinetically favored smaller of the two possible rings (lactone or lactam), although for the substrates derived originally from iodoalanine approximately 10% of a minor regioisomer was observed in the crude reaction mixture. The lactam amides derived from **3** were formed as equimolar mixtures of diastereomers (Table 2, entries 5 and 6), in keeping with the nature of **3** itself. Interestingly, when the (3-*tert*-butyloxycarbonyl)thiosuccinic anhydride **12** was subjected to the deprotection, cyclization sequence and the resulting thiocarboxylate trapped with *N*-(2-phenylethyl)-dinitrobenzenesulfonamide the expected product was not the amido lactone **26** but rather the imide **27**. This product was isolated in 74% yield and arises from cyclization of the amide onto the δ-lactone functionality (Table 2, entry 12). This result stands in contrast to that of Table 2, entry 10, for which the substrate was the lower homologue **11** and when the expected γ-lactone **24** was readily isolated and characterized. The difference in reactivity of the two lactones toward the side-chain amide group, however, is in complete agreement with the general pattern according to which δ-valerolactones are considerably more susceptible to alkaline hydrolysis than the γ-butyrolactones[8] and the general greater stability of γ- rather than δ-lactones in the uronic acid series.[9]

In a second set of experiments, substrates **8** and **10**, after removal of the Boc group and cyclization, were treated with 5-iodo-1-pentyne to give the pentynyl thioesters **28** and **29** (Table 3, entries 1 and 2), setting the scene for application of the Spagnolo method[10] for acyl radical formation and capture. One example was quenched with 1,4-diiodobutane to give the iodobutyl thioester **30** (Table 3, entry 3).

Treatment of the two pentynyl thioesters with thiophenol and AIBN in benzene at 80 °C, according to the method of Spagnolo and co-workers,[10] resulted in the formation of the aldehydes **31** and **32** in good yield (Table 4, entries 1 and 2). Alternatively, **28** was treated under the same conditions with the electron-deficient allyl phenyl sulfide **33**[11] resulting in homologation of the

TABLE 1. Radical Addition Reactions



Entry	Iodide	Adduct, % yield
1	 **1**	 **7**, 86
2	 **2**	 **8**, 92
3	 **3**	 **9**, 85
4	 **4**	 **10**, 70
5	 **5**	 **11**, 79
6	 **6**	 **12**, 82

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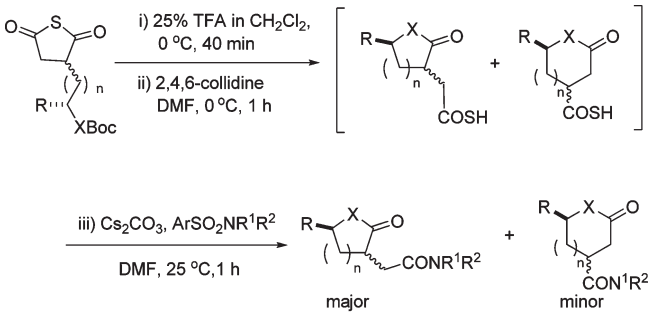
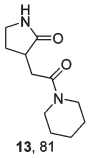
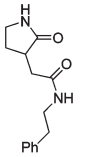
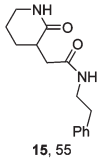
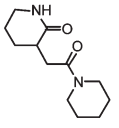
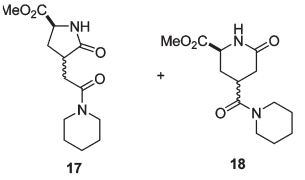
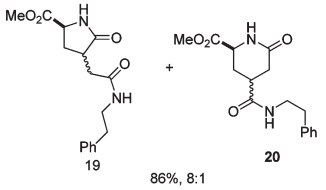
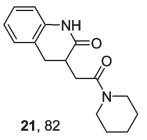
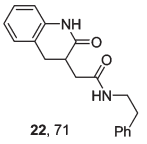
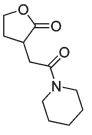
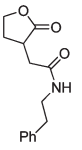
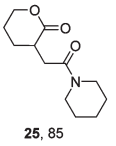
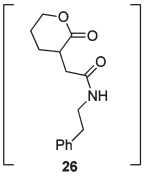
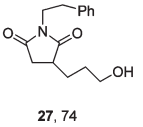
(11) Barton, D. H. R.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1613–1619.

TABLE 2. Cyclization with Subsequent Amide Bond Formation



R = H, CO_2Me; X = NH, O; n = 1, 2; Ar = 2,4-dinitrophenyl

Entry	Subs.	R^1R^2NH	Products, % yield
1	**7**	piperidine	 **13**, 81
2	**7**	$Ph(CH_2)_2NH_2$	 **14**, 57
3	**8**	$Ph(CH_2)_2NH_2$	 **15**, 55
4	**8**	piperidine	 **16**, 75
5	**9**	piperidine	 **17** + **18** 69%, 10:1
6	**9**	$Ph(CH_2)_2NH_2$	 **19** + **20** 86%, 8:1
7	**10**	piperidine	 **21**, 82
8	**10**	$Ph(CH_2)_2NH_2$	 **22**, 71
9	**11**	piperidine	 **23**, 72
10	**11**	$Ph(CH_2)_2NH_2$	 **24**, 71
11	**12**	piperidine	 **25**, 85
12	**12**	$Ph(CH_2)_2NH_2$	 **26**  **27**, 74

thioester to the ketone **34** in good yield (Table 4, entry 3). These reactions proceed via a mechanism involving homolytic addition of the phenylthiyl radical to the terminal position of the alkyne generating a vinyl radical, which undergoes intramolecular homolytic substitution on the thioester to give the acyl radical. With thiophenol, chain transfer is achieved by hydrogen atom transfer, whereas with the allyl sulfide propagation is the result of an homolytic allylic displacement process.

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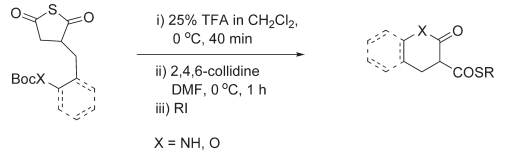
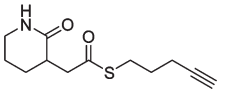
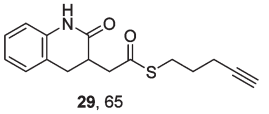
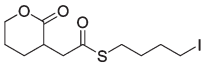
TABLE 3. Cyclization with Thioester Formation



Entry	Subs.	Alkyl halide	Product
1	**8**	5-iodopentyne	 **28**, 69
2	**10**	5-iodopentyne	 **29**, 65
3	**12**	1,4-diiodobutane	 **30**, 61

Finally, under the conditions of Liebeskind and co-workers,[12] the iodobutyl thioester **30** was treated with phenylboronic acid in the presence of copper thiophenecarboxylate, bis(dibenzylideneacetone)palladium(0), and tris(*o*-tolyl)phosphine to give the phenyl ketone **35** in 70% yield (Scheme 1).

Overall, thiomaleic anhydride has been shown to be a convenient trap for functionalized alkyl radicals with the adducts serving as precursors to a variety of thioacids substituted with lactams and lactones. The so-formed thioacids may be trapped by a variety of reactions including amide bond formation with electron-deficient sulfonamides and alkylation leading to thioesters. These thioesters may in turn be applied in further radical or organometallic coupling processes.

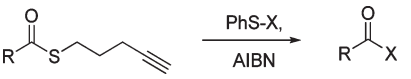
Experimental Section

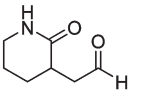
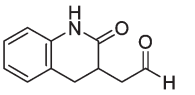
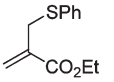
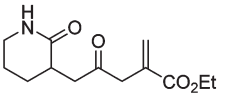
General Procedure for Free-Radical Addition to Monothiomaleic Anhydride. Tris(trimethylsilyl)silane (373 mg, 1.5 mmol) and AIBN (33 mg, 0.2 mmol) in dry degassed toluene (3 mL) were added dropwise to a stirred mixture of alkyl iodide (1 mmol) and thiomaleic anhydride (228 mg, 2 mmol) in dry degassed toluene (5 mL) at 90 °C over 3 h by syringe pump under a N_2 atmosphere. Simultaneously, thiomaleic anhydride (342 mg, 3 mmol) in dry degassed toluene (2 mL) was added to the reaction mixture separately by syringe pump over 3 h. When the addition was complete, the reaction mixture was allowed to stir for an additional 1 h at 90 °C before it was cooled to room temperature, and the solvent was removed under vacuum. Purification was achieved by rapid chromatography of the concentrate over silica gel that had been prewashed with acetone followed by hexanes.[13]

2-[(2-*tert*-Butyloxycarbonylaminophenyl)methyl]thiosuccinic Anhydride (10). Rapid chromatographic purification over silica gel, prewashed with acetone followed by hexanes, eluting with 30% EtOAc/hexanes afforded a colorless oil in 70% yield: IR (film) 1708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.5 Hz, 1H), 7.30−7.26 (m, 1H), 7.13 (dd, J = 1, 5 Hz, 2H), 6.45 (br s, 1H), 3.58−3.51 (m, 1H), 3.33 (dd, J = 4.5, 14.5 Hz, 1H), 3.07 (dd, J = 8.5, 18.0 Hz, 1H), 2.91 (dd J = 8.5, 14.5 Hz, 1H), 2.88 (dd, J = 7.0, 18.0 Hz, 1H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 198.4, 153.8, 136.2, 130.5, 129.7, 128.5, 125.6, 125.1, 81.1, 53.1, 46.5, 32.5, 28.5; ESIHRMS *m*/*z* calcd for $C_{16}H_{19}NO_4SNa$ $(M + Na)^+$ 344.0932, found 344.0930.

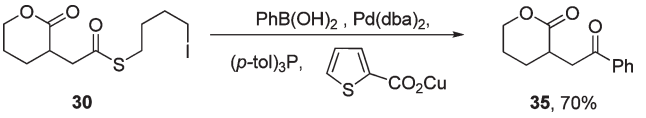
General Procedure for Heterocycle Synthesis from the Radical Adducts. To a stirred solution of the radical adduct (1 mmol) in dichloromethane (20 mL) at 0 °C was added TFA (5 mL) dropwise. Stirring was maintained for 40 min before TFA was removed by azeotropic distillation with toluene (5 mL×3), after which the residue was dried under vacuum. For amino thioanhydrides, the residue was dissolved in DMF (20 mL) and cooled to 0 °C before 2,4,6-collidine (182 mg, 1.5 mmol) was dropwise added, and the reaction mixture was stirred for 1 h at 0 °C. For hydroxy thioanhydrides, the residue was dissolved in DMF (20 mL), and the reaction mixture was stirred overnight at room temperature. For both amino thioanhydrides and hydroxy thioanhydrides, the resulting reaction mixture was cooled to 0 °C, and Cs_2CO_3 (391 mg, 1.2 mmol) followed by sulfonamide (1.2 mmol) was added before the reaction mixture was warmed to room temperature and stirred for 1.5 h. The solvent was removed under vacuum, the residue was dissolved in EtOAc (50 mL), and the organic layer was washed successively with water and brine, dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

TABLE 4. Radical Chemistry of Thioesters



Entry	Subs	Propagating agent	Product
1	**28**	thiophenol	 **31**, 69
2	**29**	thiophenol	 **32**, 64
3	**28**	 **33**	 **34**, 68

SCHEME 1. Ketone Formation from an Iodobutyl Thioester



30 **35**, 70%

(12) (a) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229–3231. (b) Yang, H.; Li, H.; Wittenburg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132–1140.

(13) The silica gel was washed in this manner to remove as much water as possible and so to minimize hydrolysis of the cyclic thioanhydrides during chromatographic purification.

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***N*-[(2-Oxo-1,2,3,4-tetrahydroquinolin-3-yl)acetyl]piperidine (21).** Chromatographic purification over silica gel eluting with 4% methanol/dichloromethane afforded white needles in 82% yield: mp 138.0−138.4 °C; IR (film) 1680 and 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (br s, 1H), 7.20−7.16 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 6.73 (dd, J = 1.5, 7.5 Hz, 1H), 3.68−3.62 (m, 1H), 3.58−3.40 (m, 3H), 3.24−3.14 (m, 3H), 2.83 (t, J = 15.2 Hz, 1H), 2.44−2.38 (m, 1H), 1.70−1.54 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 169.1, 137.1, 128.5, 127.7, 124.1, 123.3, 115.0, 46.8, 43.1, 37.1, 33.2, 31.8, 29.9, 26.7, 25.8, 24.8; m/z calcd for $C_{16}H_{20}N_2O_2Na$ $(M + Na)^+$ 295.1422, found 295.1434.

General Procedure for Thioester Synthesis from the Radical Adducts. TFA (5 mL) was added dropwise to a stirred solution of thioanhydride (1 mmol) in dicholoromethane (20 mL) at 0 °C. After the mixture was stirred for 40 min, toluene (5 mL) was added and then removed under vacuum. Two further portions of toluene (5 mL each) were added and stripped off under vacuum, and the residue was dried under vacuum. For amino thioanhydrides, the residue was dissolved in DMF (20 mL) and cooled to 0 °C before 2,4,6-collidine (182 mg, 1.5 mmol) was dropwise added and the mixture stirred for 1 h at 0 °C. For hydroxy thioanhydrides, the residue was dissolved in DMF (20 mL), and the reaction mixture was stirred overnight at room temperature. For both amino thioanhydrides and hydroxy thioanhydrides, the resulting reaction mixture was cooled to 0 °C, and alkyl iodide (4 mmol) in DMF (2 mL) was dropwise added followed by triethylamine (102 mg, 1 mmol) followed by stirring for 5 h at room temperature. The solvent was removed under vacuum, the residue was dissolved in EtOAc (50 mL), and the organic layer was successively washed with water and brine, dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

General Procedure for Aldehyde Synthesis from *S*-Pentynylthioesters. Thiophenol (34 mg, 0.30 mmol) and AIBN (10 mg, 0.06 mmol) in dry degassed benzene (3 mL) was dropwise added to a refluxing solution of *S*-pentenylthioester (0.15 mmol) in dry degassed benzene (3 mL) over 3 h. The reaction mixture was stirred for an additional 6 h at reflux before the solvent was removed under vacuum and the residue purified by column chromatography over silica gel.

Ethyl 2-Methylen-4-oxo-5-(2-oxopiperidin-3-yl)pentanoate (34). Thioester **28** (44 mg, 0.184 mmol) and ethyl 2-(phenylthiomethyl)-acrylate (82 mg, 0.37 mmol) were heated to reflux with stirring in benzene (4 mL), and a mixture of thiophenol (10 mg, 0.09 mmol) and AIBN (15 mg, 0.09 mmol) in benzene (4 mL) was added over 7 h by syringe pump. Stirring was continued for 3 h before the solvent was removed under vacuum and the residue purified by chromatography over silica gel eluting with 4% methanol/dichloromethane to afford a colorless oil in 68% yield: ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (s, 1H), 5.69 (br s, 1H), 5.67 (s, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.45 (d, J = 4.0 Hz, 1H), 3.44−3.28 (m, 2H), 3.09 (dd, J = 4.0, 17.0 Hz, 1H), 2.84−2.76 (m, 2H), 2.73 (dd, J = 7.5, 17.5 Hz, 1H), 2.04−1.98 (m, 1H), 1.92−1.86 (m, 1H), 1.84−1.75 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 174.1, 166.6, 134.6, 128.9, 61.2, 46.2, 44.1, 42.8, 37.7, 27.1, 22.4, 14.4; ESIHRMS m/z calcd for $C_{13}H_{19}NO_4Na$ $(M + Na)^+$ 276.1212, found 276.1225.

3-(2-Oxo-2-phenylethyl)tetrahydro-2*H*-pyran-2-one (35). Thioester **30** (36 mg, 0.1 mmol), $PhB(OH)_2$ (19 mg, 0.15 mmol), copper(I) thiophene-2-carboxylate (32 mg, 0.17 mmol), tris-*p*-tolylphosphine (1.2 mg, 0.004 mmol), and bis(dibenzylideneacetone)palladium(0) (1.2 mg, 0.002 mmol) were mixed in dry THF (5 mL) and heated to 55 °C with stirring for 60 h under N_2 gas. The solvent was removed under vacuum and the residue purified by chromatography over silica gel eluting with 40% EtOAc/hexanes to afford a colorless oil in 70% yield: ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 4.46 (t, J = 5.7 Hz, 2H), 3.62 (dd, J = 3.7, 18.2 Hz, 1H), 3.29 (dd, J = 6.7, 18.2 Hz, 1H), 3.20−3.14 (m, 1H), 2.23−2.16 (m, 1H), 2.03−1.94 (m, 2H), 1.71−1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 174.4, 136.8, 133.6, 128.9, 128.3, 68.9, 40.4, 35.8, 25.4, 22.7; ESIHRMS m/z calcd for $C_{13}H_{14}O_3Na$ $(M + Na)^+$ 241.0841, found 241.0820.

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Supporting Information Available: Complete experimental details for the formation and characterization of compounds **1**−**6** and full characterization data for compounds **7**−**9**, **11**−**20**, **22**−**25**, and **27**−**32**. Copies of the ^1H and ^{13}C spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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