Full Paper

CSIRO PUBLISHING

Aust. J. Chem. **2005**, *58*, 864–869

www.publish.csiro.au/journals/ajc

Synthesis of Some 4-Oxothiochromenes and Related Compounds

Andris J. Liepa,[A,B] *Oanh Nguyen*,[A] *and Simon Saubern*[A]

[A] CSIRO Molecular and Health Technologies, Clayton South VIC 3169, Australia.
[B] Corresponding author. Email: andy.liepa@csiro.au

Thiosalicylic acids react with 2-substituted *N*,*N*-dialkyl acetamides to give 3-substituted-*N*,*N*-dialkyl-2-amino-4-oxothiochromenes **13**. *N*-Alkyl 2-piperidone and analogous caprolactams give derivatives of 1,2,3,4-tetrahydrothiochromeno[2,3-*b*]pyridin-5-one **16a**–**16d** and 7,8,9,10-tetrahydro-6*H*-5-thia-6-aza-cyclohepta-[*b*]-naphthalen-11-one **16e**, **16f**. 2-Mercaptonicotinic acid gave a 1,2,3,4-tetrahydro-9-thia-1,8-diazaanthracen-10-one **16g** and a 1,2,3,4-tetrahydro-9-thia-1,8-diazaanthracene-10-thione **16h**.

Manuscript received: 5 August 2005.
Final version: 25 October 2005.

Introduction

The search for useful biological activity relies upon a continuing supply of novel molecules, especially those with moderate molecular weight and specific properties.[1] Providing a stream of synthetic molecules that are novel yet readily accessible presents a formidable ongoing challenge in synthetic chemistry. Time and cost place constraints on the selection of eligible starting materials. Conversely, there is a continuing need for innovative synthesis strategies with which to provide access to uncommon structural domains. In this context, thiochromones are of potential interest since they manifest various forms of biological activity.[2]

Among such thiochromones, those bearing an amino substituent in the 2-position are relatively rare. The few known representatives have most commonly been prepared by reaction of a 2-bromothiochroman with an amine.[3]

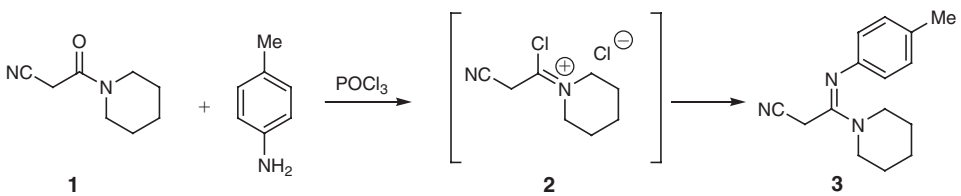
In order to increase product diversity within this domain, it is beneficial to investigate a synthesis pathway alternative to those already described in the chemical literature. Preferably, this route would enable a nitrogen-containing substituent to be incorporated at an early stage in the synthesis, such as during assembly of the thiochroman ring. Retrosynthetic analyses suggest that amides are prominent among the alternative amine-related compounds for prospective starting materials. This compound class is readily available, is diverse and is amenable to chemical activation. For example, it is well known that many tertiary amides can be activated by reaction with phosphorus oxychloride to form electrophilic iminium halides. Among the numerous applications for such active intermediates is the conversion of a cyanoacetamide (**1**, Scheme 1) into an amidine **3**.[4]

It is possible that *p*-toluidine can react with a mild carbon-centred electrophile (iminium halide, a probable intermediate, **2** Scheme 1) even in the presence of a strongly electrophilic phosphorus-centred reagent (phosphorus oxychloride). Further, cyanoacetamides contain an activated methylene group that is potentially susceptible to electrophilic attack. It was realized that the presence of such potential for both electrophilic and nucleophilic reactivity might be exploited to provide a simple one-step synthesis of the desired 2-aminothiochromans.

Mercapto groups are powerful nucleophiles that retain some nucleophilicity within the strongly acidic/electrophilic environment in the presence of phosphorus oxychloride. In the presence of a suitably located carboxylic acid group, a thiochromene could result from the initial tethering of a mercaptan to the iminium chloride of **4** (Scheme 2) followed by acylation of the activated methylene group. The required configuration of reactive groups is evident within thiosalicylic acid **5** (Scheme 2).

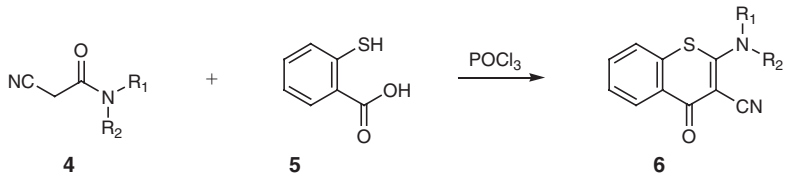
Results and Discussion

In order to broaden the scope of the proposed synthesis the supply of substituted thiosalicylic acids was diversified.

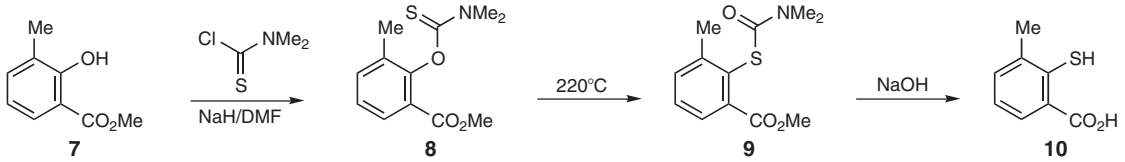


Scheme 1.

10.1071/CH05205 0004-9425/05/120864



Scheme 2.



Scheme 3.

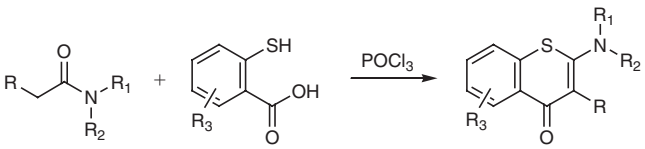
Such compounds have been prepared[5] by diazotization of substituted anthranilic acids followed by displacement of nitrogen with a suitable sulfur nucleophile. Alternatively, a method[6] has been developed for converting phenols into the corresponding mercaptans based upon a thermal rearrangement of an *N*,*N*-dimethyl thiocarbamate. Since a variety of salicylic acids is readily available, an investigation of the applicability of this methodology to the conversion of salicylic acids into their thio analogues was of interest. Treating *N*,*N*-dimethylthiocarbamoyl chloride with the sodium salt of methyl 2-hydroxy-3-methylbenzoate **7** (Scheme 3) in *N*,*N*-dimethylformamide at 80°C gave the corresponding crude thiocarbamate **8** (Scheme 3) in 59% yield.

Heating the thiocarbamate **8** (Scheme 3) in triethyleneglycol dimethyl ether (triglyme) at the boiling point for 24 h then gave a moderate yield of the rearranged material **9** (Scheme 3) (53% of crude product). Although a longer period at reflux consumed more of the starting material, this process also led to an increase in by-products. The technique of heating by microwave may benefit reactions requiring high temperature by decreasing the time required, as well as diminishing by-product formation. It was found that when methyl 2-*N*,*N*-dimethylcarbamoyloxy-3-methyl benzoate **8** was heated in triglyme in a microwave oven at 250°C for 60 min a 79% yield of **9** (estimated by ^{1}H NMR spectroscopy) was obtained. Hydrolysis then gave thiosalicylic acid **10**.

Thiosalicylic acid reacted readily with the cyanoacetamide **11a** in refluxing 1,2-dichloroethane in the presence of excess of phosphorus oxychloride, to form 2-pyrrolidino-4-oxo-4*H*-thiochromene **13a** (Table 1) in 44% yield. A described previously,[7] pyridine 6-chloro-2,4-dipyrrolidin-1-ylnicotinonitrile was also obtained in 46% yield because of self-condensation of the cyanoacetamide **11a**.

Although 1,2-dichloroethane was chosen as solvent for the initial condensation, it was later found that acetonitrile gave better results, and most of the subsequent reactions were carried out in this medium. Under these conditions self-condensation of the cyanoacetamide **11a** was not observed. This new condensation protocol (Table 1) was useful in providing modest yields of the 2-dialkylaminothiochromenes **13a** and **13b** (Table 1) while simultaneously establishing a cyano substituent in the 3-position.

Table 1. Preparation of 2-amino-4-oxo-4*H*-thiochromenes

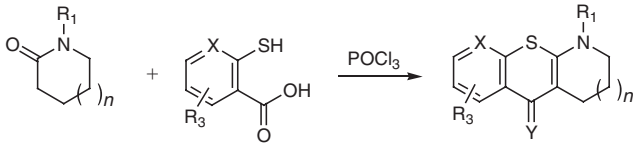


11 **12** **13**

	R **11**	R_1 **11**	R_2 **11**	R_3 **12**	R_3 **13**	Yield [%]
a	CN	-$(CH_2)_4$-		H	H	44
b	CN	-$(CH_2)_4$-		5-Cl	6-Cl	36
c	CO_2Me	-$(CH_2)_4$-		4-Cl	7-Cl	64
d	CO_2Et	-$(CH_2)_4$-		3-Me	8-Me	63
e	CO_2Me	-$(CH_2)_5$-		H	H	66
f	CO_2Et	-$(CH_2)_5$-		4-Cl	7-Cl	32
g	Cl	-$CH_2C(Me)_2(CH_2)_3$-		—	—	
h	Cl	Et	Et	—	—	
i	SO_2Ph	-$CH_2C(Me)_2(CH_2)_3$-		H	H	55
j	SO_2Ph(4-Me)	Et	Et	H	H	53

It was evident that activation of the methylene group in **11**, presumably a requirement to enable condensation to occur, might also be affected by electron-withdrawing substituents other than nitrile in the 2-position of the *N*,*N*-dialkylacetamide precursors **11**. Such a modification would also provide opportunities for variation of the substituent in the 3-position of the resulting thiochromenes **13**. In order to evaluate the ability of an ester moiety to achieve such activation in place of a nitrile, a series of malonamides **11c**–**11f** (Table 1) was prepared by transamination of malonic esters with either pyrrolidine or piperidine. These precursors also condensed readily with thiosalicylic acids **12** to form the corresponding thiochromene esters **13c**–**13f**. Aryl sulfonyl substituents could also be introduced into the 3-position without difficulty. Thus, treatment of chloroacetamides **11g** and **11h** (Table 1) with sodium benzene or sodium *p*-toluene sulfinate, respectively, gave the 2-arylsulfonyl acetamides **11i** and **11j**. These compounds also condensed with thiosalicylic

Table 2. Preparation of tricyclic thiochromenes



14 **15** **16**

	R_1 **14**	*n*	X	Y	R_3 **15**, **16**	Yield [%]
a	Me	1	CH	O	H, H	37
b	Pr	1	CH	O	H, H	69
c	Et	1	CH	O	4-Cl, 8-Cl	21
d	(2-Cl)$PhCH_2$	1	CH	O	4-Cl, 8-Cl	26
e	Me	2	CH	O	H, H	28
f	(4-Cl)$PhCH_2$	2	CH	O	H, H	15
g	$PhCH_2$	1	N	O	H, H	29
h	$PhCH_2$	1	N	S	H, H	14

acid to give the corresponding 3-arysulfonyl thiochromenes **13i** and **13j**.

With variations in the substituent at the 3-position demonstrated, the effect of varying substituents in the thiosalicylic acid moiety upon the cyclization was briefly examined. These condensations proceeded as expected. The presence of a methyl group adjacent to the mercapto group in the thiosalicylic acid **10** (Scheme 3) did not prevent cyclization to form **13d**.

The device of using activation by an iminium salt to enable acylation of an adjacent carbon also offered an opportunity to generate tricyclic thiochromene analogues. Thus, if an *N*-alkylated lactam was the starting material, the initially formed iminium salt should react with the mercapto group of a thiosalicylic acid. This process would give an intermediate that could be sufficiently activated to undergo an intramolecular acylation leading to formation of an additional ring. Such a condensation proceeded without difficulty, albeit slowly, in dichloromethane, and this allowed several *N*-alkylated piperidine 2-ones (**14a**–**14d**, **14g**) and caprolactams (**14e** and **14f**) to be converted into the corresponding tricyclic products (Table 2). However, attempts to similarly use *N*-alkylated pyrrolidin-2-ones did not produce tricyclic material that could be isolated when treated with either thiosalicylic acid or 2-mercaptonicotinic acid. When a reaction was carried out between 1-benzyl-2-piperidone and 2-mercaptonicotinic acid **15** (X = N, R_3 = H) in sulfolane, a small amount (14%) of the thione analogue **16h** of the anticipated product **16g** was obtained with only a trace of **16g** being formed. This product selectivity was reversed when 1-benzyl-2-piperidone was first reacted overnight with an excess of phosphorus oxychloride and then treated with 2-mercaptonicotinic acid. Under these conditions a 29% yield of **16g** was isolated and a very small amount of the thione **16h** was observed. The reactions that produce the thione **16h** have not been investigated, but thione may result from formation of an imidoyl chloride from the vinylogous amide **16g**, followed by reaction with 2-mercaptonicotinic acid and subsequent cleavage of the pyridine–sulfur bond.

Experimental

Materials and Methods

Light petroleum is the 40–60°C-bp fraction. Unless specified, ^1H and ^{13}C NMR spectra were recorded on a Bruker Av400 spectrometer at 400 MHz and 100.6 MHz, respectively, using $CDCl_3$ solutions. Chemical shifts are measured in ppm. Mass spectra were recorded on a Fisons Instruments VG Platform quadrupole using either atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) in the positive- and/or negative-ion mode with a cone voltage of 30 eV for both APCI and ESI, using either 1/1 acetonitrile/water or methanol as solvent. Microanalyses were performed by the Campbell Microanalytical Laboratory, University of Otago. Melting points were recorded on a Reichert-Kofler hot-stage micro-melting point apparatus, and are uncorrected. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh; particle size 0.04–0.63 mm) silica gel. Radial chromatography was performed with silica gel (60 PF_{254}) coated glass rotors by means of a Harrison Research Chromatotron (Model 7924T). Analytical thin-layer chromatography (TLC) was conducted on Sigma–Aldrich silica gel on polyester sheets with ultraviolet indicator. Microwave heating was carried out in a BIOTAGE 'Initiator' 60.

*Methyl 3-Oxo-3-pyrrolidin-1-yl-propionate **11c** and Methyl 3-Oxo-3-piperidin-1-yl-propionate **11e***

A mixture of dimethyl malonate (1 mol), benzene (200 mL), and the amine (1.1 mol) was stirred for 2 h then refluxed for 48 h. The easily volatilized components were removed using a rotary evaporator, and the respective residues were fractionally distilled to give the following. Methyl 3-oxo-3-pyrrolidin-1-yl-propionate, bp 110–113°C (0.2 mm, 62%). (Found: C 56.2, H 7.4, N 8.1. $C_8H_{13}NO_3$ requires C 56.1, H 7.65, N 8.2%). δ_H 1.85 (4H, m, $NCH_2CH_2CH_2$), 3.33 (2H, s, $COCH_2$), 3.42 (4H, m, CH_2NCH_2), 3.66 (3H, s, CH_3). Methyl 3-oxo-3-piperidin-1-yl-propionate, 109–112°C (0.5 mm, 73% yield). (Found: C 58.2, H 8.1, N 7.4%. $C_9H_{15}NO_3$ requires C 58.4, H 8.2, N 7.6%). δ_H 1.58 (6H, m, $NCH_2CH_2CH_2CH_2$), 3.34 (2H, m, NCH_2), 3.43 (2H, s, $COCH_2$), 3.58 (2H, m, CH_2N), 3.73 (3H, s, CH_3).

*2-Mercapto-3-methylbenzoic Acid **10** from 2-Dimethylthiocarbamoyloxy-3-methylbenzoate **8***

Sodium hydride (150 mg, 50% in oil) was added to a solution of methyl 2-hydroxy-3-methyl benzoate (500 mg, 3.0 mmol) in *N*,*N*-dimethylformamide (15 mL). The suspension was heated to 80°C before adding dimethylthiocarbamoyl chloride (450 mg, 3.6 mmol). The reaction mixture was heated for 2 h at 80°C then cooled on ice. Water (60 mL) was added and the solution extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated to form a yellow oil. Flash chromatography using ethyl acetate/petroleum spirits (1/1) as eluent provided methyl 2-dimethylthiocarbamoyloxy-3-methylbenzoate **8** (450 mg, 59%) as an oil that solidified on standing. Recrystallization (light petroleum) gave a pale tan *solid*, mp 103–104°C (Found: C 56.6, H 6.0, N 5.75, S 12.5. $C_{12}H_{15}NO_3S$ requires C 56.9, H 6.0, N 5.5, S 12.7%). δ_H 2.25 (3H, s, 3-Me), 3.48, 3.41 (3H each, each s, NMe_2), 3.83 (3H, s, CO_2Me), 7.21 (1H, t, *J* 7.7, H5), 7.43 (1H, dd, *J* 7.7, 1.8, H4), 7.85 (1H, dd, *J* 7.7 and 1.8, H6). The thiocarbamate **8** (470 mg) was dissolved in triethyleneglycol dimethyl ether (10 mL), the solution was degassed, placed in a pre-heated oil bath (220°C), and stirred under nitrogen until TLC analysis (1/1 light petroleum/ethyl acetate) confirmed the starting material was fully rearranged (typically 24 h). The reaction was cooled to room temperature, diluted with water (80 mL) and extracted with toluene (3 × 30 mL). The combined extracts were washed with brine (3 × 50 mL) and concentrated. Flash chromatography using ethyl acetate/light petroleum (1/1) as eluent provided crude methyl (2-dimethylcarbamoylsulfanyl-3-methyl) benzoate **9** (240 mg, 53%) as an oil. δ_H 2.44 (3H, s, 3-Me), 3.09 (6H, br s, NMe_2), 3.84 (3H, s, CO_2Me), 7.31 (1H, t, *J* 7.7, H5), 7.43 (1H, dd, *J* 1.8, 7.7, H4), 7.56 (1H, dd, *J* 1.8, 7.7, H6). The oil was dissolved in a mixture of methanol (5 mL) and aqueous sodium hydroxide (2.5 equiv. NaOH, 1 mL) then the solution was heated at reflux for 8 h under nitrogen. The reaction was cooled to room temperature, diluted

with water (20 mL), and washed with dichloromethane (3 × 10 mL). The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid then extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated giving 2-mercapto-3-methylbenzoic acid (90 mg, 56%) as a white powder, mp 157–159°C (lit.[8] 155–157°C). δ_H 2.40 (3H, s, 3-Me), 6.54 (1H, s, SH), 7.09 (1H, t, *J* 7.5, H5), 7.36 (1H, d, *J* 7.5, H4), 8.04 (1H, d, *J* 7.5, H6).

Preparation of 5-Chloro-2-mercaptobenzoic Acid

A solution of methyl 5-chloro-2-hydroxybenzoate (5.0 g) in *N*,*N*-dimethylformamide (20 mL) was treated with excess sodium hydride (1.3 g, 50% in oil). The suspension was heated to 80°C before adding *N*,*N*-dimethylthiocarbamoyl chloride (5.0 g, 1.5 equiv.). Heating of the reaction mixture was continued for 2 h before cooling on ice. The reaction mixture was diluted with water (50 mL), then extracted into toluene (3 × 50 mL). The combined extracts were concentrated to form a viscous orange oil. The oil was diluted with triethyleneglycol dimethyl ether (50 mL), the solution was degassed, the reaction mixture was then placed in a pre-heated sand bath and heated to a gentle reflux for 4 h under nitrogen. The solution was cooled, treated with aqueous sodium hydroxide (2.5 M, 30 mL), and stirred at room temperature for 16 h under nitrogen. The reaction mixture was cooled to 0–5°C, and acidified to pH 1 with concentrated hydrochloric acid to form an off-white precipitate. The solid was filtered off, washed with water, and dried to afford 5-chloro-2-mercaptobenzoic acid (3.95 g, 78% overall). δ_H 7.28 (1H, d, *J* 8.3, H3), 7.35 (1H, dd, *J* 8.3 and 2.2, H4), 8.11 (1H, d, *J* 2.2, H6). mp 192–194°C (lit.[9] 193–194°C).

*4-Oxo-2-pyrrolidin-1-yl-4*H*-thiochromene-3-carbonitrile* ***13a***

A mixture of 2-mercaptobenzoic acid (0.51 g, 3.3 mmol), phosphorus oxychloride (1.0 g, 6.6 mmol) and 3-oxo-3-pyrrolidin-1-yl-propionitrile (0.46 g, 3.3 mmol) in 1,2-dichloroethane (12 mL) was heated at reflux for 4 h. The solution was cooled, stirred with water (30 mL) for 4 h, and adjusted to pH 9 by portion-wise addition of solid potassium carbonate. The material obtained after evaporation of the organic layer was chromatographed over silica gel with elution by dichloromethane followed by 10% ethyl acetate in dichloromethane to afford two major products. The first was 6-chloro-2,4-dipyrrolidin-1-yl-nicotinonitrile (105 mg, 46%),[7] mp 128–130°C (lit. 129–131°C). δ_H 1.8–2.2 (8H, m, pyrrolidine H), 3.4–3.8 (8H, m, pyrrolidine H), 6.00 (s, 1H, pyridine H). δ_C 25.5 (4 × CH_2, overlapping), 49.8 (2 × NCH_2), 50.3 (2 × NCH_2), 72.6, 96.9, 119.0, 152.7, 158.3, 160.4. Evaporation of the later fractions gave a pale yellow solid that was recrystallized from acetonitrile to afford the *product* **13a** as white fluffy needles (0.37 g, 44%), mp 236–237°C. (Found: C 65.5, H 4.7, N 11.1, S 12.4. $C_{14}H_{12}N_2OS$ requires C 65.6, H 4.7, N 10.9, S 12.5%). ν_{max} (KBr)/cm^{-1} 2204 (CN). δ_H 2.10 (4H, m, $NCH_2CH_2CH_2$), 3.89 (4H, m, CH_2NCH_2), 7.30–7.51 (3H, m, 3ArH), 8.42 (1H, dd, *J* 1.8, 9.5, ArH). δ_C 25.5 (CH_2CH_2N), 52.5 (CH_2N), 85.3 (C3), 118.0 (CN), 125.0 (C8), 127.6 (C7), 128.3 (C8a), 128.5 (C5), 130.9 (C4a), 131.7 (C6), 162.4 (C2), 178.3 (C4). *m*/*z* (APCI) 257.2 $[M + H]^+$.

*6-Chloro-4-oxo-2-pyrrolidin-1-yl-4*H*-thiochromene-3-carbonitrile* ***13b***

This product was prepared in an analogous manner to **13a** and recrystallized from chloroform/ethanol to give the *product* **13b** as pale yellow shiny crystals (36%), mp 281–282°C. (Found: C 57.7, H 3.6, N 9.7, S 10.9. $C_{14}H_{11}ClN_2OS$ requires C 57.8, H 3.8, Cl 12.2, N 9.6, S 11.0%). ν_{max} (KBr)/cm^{-1} 2195. δ_H 2.14 (4H, m, 4cycpentH), 3.92 (4H, m, 4cycpentH), 7.30 (1H, d, *J* 8.8, ArH), 7.45 (1H, dd, *J* 2.2, 8.8, ArH), 8.30 (1H, d, *J* 2.2, ArH). δ_C (125 Mz) 25.6, 53.5, 84.9 118.0, 126.7, 128.5, 128.7, 129.3, 133, 135, 163.8, 178.9. *m*/*z* (APCI) 291.2 $[M + H]^+$.

*Methyl 7-Chloro-4-oxo-2-pyrrolidin-1-yl-4*H*-thiochromene-3-carboxylate* ***13c***

A mixture of 4-chloro-2-mercaptobenzoic acid[9] (381 mg, 2 mmol) and ethyl 3-oxo-3-pyrrolidin-1-yl-propionate (370 mg, 2 mmol) in acetonitrile (5 mL) was heated to 60°C and treated with phosphorus oxychloride (610 mg, 4 mmol). The reaction was stirred for 3 h, cooled to room temperature and quenched with saturated aqueous sodium bicarbonate (2 mL). The reaction was extracted with ethyl acetate (3 × 5 mL), and the combined extracts were filtered through a small plug of silica gel. The filtrate was concentrated to afford an orange solid (430 mg, 64%) that was recrystallized from ethanol to give the *product* **13c** as granular orange crystals, mp 225–227°C. (Found: C 55.8, H 4.4, N 4.5, S 9.8. $C_{15}H_{14}ClNO_3S$ requires C 55.6, H 4.4, N 4.3, S 9.9%). δ_H 1.99 (4H, m, $NCH_2CH_2CH_2$), 3.49 (4H, m, CH_2NCH_2), 3.89 (3H, s, Me), 7.32–7.37 (3H, m, 2ArH), 8.31 (1H, d, *J* 9.1, ArH). δ_C 25.4, 50.6, 52.6, 107.4, 124.0, 127.5, 128.0, 129.8, 133.6, 137.0, 155.4, 169.3, 176.6. *m*/*z* (APCI) 324.1, 326.1 $[M + H]^+$.

*Ethyl 8-Methyl-4-oxo-2-pyrrolidin-1-yl-4*H*-thiochromene-3-carboxylate* ***13d***

A mixture of 3-methyl-2-mercaptobenzoic acid (90 mg, 0.54 mmol) and ethyl 3-oxo-3-pyrrolidin-1-yl-propionate (100 mg, 0.540 mmol) in acetonitrile (5 mL) was heated to 60°C and treated with phosphorus oxychloride (100 μL, 1.1 mmol) to afford a yellow solid (107 mg, 63%), mp 189–192°C. Recrystallization from ethyl acetate gave the *product* **13d** as yellow crystals, mp 202–204°C. (Found: C 64.2, H 6.2, N 4.5, S 9.9. $C_{17}H_{19}NO_3S$ requires C 64.3, H 6.0, N 4.4, S 10.1%). δ_H 1.41 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.98–2.08 (4H, m, 2-NCH_2CH_2), 2.44 (3H, s, 8-Me), 3.55–3.65 (4H, m, 2-NCH_2), 4.40 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 7.35–7.33 (2H, m, H5 and H7), 8.33 (1H, m, H6). δ_C 14.0, 18.9, 25.4, 50.5, 61.5, 107.4, 126.0, 126.1, 129.6, 131.3, 131.9, 132.9, 154.6, 169.1, 177.7.

*Methyl 4-Oxo-2-piperidin-1-yl-4*H*-thiochromene-3-carboxylate* ***13e***

Phosphorus oxychloride (1.17 mL, 12.5 mmol) was added to a stirred suspension of 2-mercaptobenzoic acid (0.77 g, 5.0 mmol) and methyl 3-oxo-3-piperidin-1-yl-propionate (1.0 g, 6.0 mmol) in acetonitrile (10 mL). The mixture was stirred at room temperature for 10 min, then heated at 70°C for 2 h. The yellow suspension, which formed a homogenous dark red solution during heating, was then cooled, poured into water (10 mL), and neutralized with solid potassium carbonate (1–2 g). After 5 min, the solids were collected, washed with water then ether to give the crude thiochromene (1.0 g, 66%) as an orange solid, mp 143–146°C. A portion was recrystallized from ethyl acetate after passing it through a plug of silica to give **13e** as *orange crystals*, mp 145–146°C. (Found: C 63.5, H 5.8, N 4.8, S 10.6. $C_{16}H_{17}NO_3S$ requires C 63.3, H 5.7, N 4.6, S 10.6%). ν_{max} (KBr)/cm^{-1} 1724 (CO_2Me). δ_H 1.69 (6H, m, piperidine H), 3.46 (4H, m, piperidine H), 3.91 (3H, s, Me) 7.40–7.56 (3H, m, 3ArH), 8.40 (1H, dd, *J* 1.1, 8.41, ArH). δ_C 23.8, 25.7, 52.3, 52.6, 113.1, 125.3, 127.2, 128.6, 130.0, 131.2, 132.5, 161.9, 168.4, 178.2. *m*/*z* (APCI) 304 $[M + H]^+$.

*Ethyl 7-Chloro-4-oxo-2-piperidin-1-yl-4*H*-thiochromene-3-carboxylate* ***13f***

Similarly, **13f** was prepared from 4-chloro-2-mercaptobenzoic acid, phosphorus oxychloride, and 3-oxo-3-piperidin-1-yl-propionic acid ethyl ester in acetonitrile yielding **13f** (32%) as an *orange oil* after chromatography over silica gel. (Found: C 57.8, H 5.4, N 4.1, S 8.9. $C_{17}H_{18}ClNO_3S$ requires C 58.0, H 5.2, N 4.0, S 9.1%). ν_{max} (neat)/cm^{-1} 1720 (CO_2Et). δ_H 1.38 (3H, t, *J* 7.3, CH_2CH_3), 1.67 (6H, m, piperidine H), 3.46 (4H, m, piperidine H), 4.36 (2H, q, *J* 7.3, CH_2CH_3), 7.40 (2H, m, 2ArH), 8.31 (1H, d, *J* 9.1, ArH). δ_C 14.2, 23.8, 25.7, 52.4, 61.7, 113.6, 124.6, 127.8, 128.4, 130.2, 134.1, 137.6, 161.2, 167.6, 177.4. *m*/*z* (APCI) 352.2, 354.2 $[M + H]^+$.

2-Benzenesulfonyl-1-(3,3-dimethylpiperidin-1-yl)ethanone ***11i***

Two equivalents of 3,3-dimethylpiperidine were treated with chloroacetyl chloride in ether at 0°C followed by a wash with water and evaporation of the solvent to give the crude chloroacetamide as an oil. δ_H (rotamer mixture, 1:1) 0.87, 0.89 (6H, s, 2 × Me), 1.55, 1.64 (4H, m, piperidine H), 3.07, 3.20 (2H, s, NCH_2CMe_2), 3.37, 3.47 (2H, m, NCH_2CH_2), 4.04, 4.07 (2H, s, $ClCH_2$). The crude product was used without purification in the following preparation.

Reaction of the crude chloroacetamide with sodium benzenesulfinate in aqueous *N*,*N*-dimethylformamide as for compound **11j** below gave the *product* **11i** (73%) as colourless needles from aqueous ethanol, mp 96–98°C. (Found: C 60.8, H 7.3, N 4.5. $C_{15}H_{21}NO_3S$ requires C 61.0, H 7.2, N 4.7%). δ_H (rotamer mixture) 0.92, 0.94 (6H, s, 2Me), 1.22, 1.43, 1.78 (4H, m, piperidine H), 3.21, 3.25 (2H, s, NCH_2CMe_2), 3.51 (2H, m, NCH_2CH_2), 4.22, 4.39 (2H, s, $COCH_2$), 7.56 (2H, m, 2 × ArH), 7.66 (1H, m, ArH), 7.93 (2H, m, ArH).

3-Benzenesulfonyl-2-(3,3-dimethylpiperidin-1-yl)thiochromen-4-one ***13i***

In a manner similar to **13c**, **13i** was prepared from 2-mercaptobenzoic acid (0.5 g, 3.4 mmol), phosphorus oxychloride (1.1 g, 7.2 mmol), and 2-benzenesulfonyl-1-(3,3-dimethylpiperidin-1-yl)ethanone (1 g, 3.4 mmol). Recrystallization from ethanol gave the *product* **13i** as white granular crystals (0.76 g, 55%), mp 259–260°C. (Found: C 63.9, H 5.8, N 3.6, S 15.6. $C_{22}H_{23}NO_3S_2$ requires C 63.9, H 5.6, N 3.4, S 15.5%). δ_H 0.99 (6H, s, 2Me), 1.53 (2H, m, piperidine H), 1.85 (2H, m, piperidine H), 3.61, 3.87 (each 2H, each m, CH_2NCH_2), 7.28–7.46 (6H, m, 6 × ArH), 7.90 (2H, dd, 7.7, 8.4, 2 × ArH), 8.02 (1H, dd, *J* 1.1, 9.1, ArH). δ_C 21.8, 22.6, 33.5, 37.0, 55.6, 67.1, 112.7, 125.4, 127.4, 127.7, 128.0, 128.4, 130.7, 131.1, 131.9, 132.0, 143.8, 165.0, 177.5. *m*/*z* (APCI) 414.2 $[M + H]^+$.

N,N-*Diethyl-2-(toluene-4-sulfonyl)acetamide* ***11j***

A mixture of 2-chloro-*N*,*N*-diethylacetamide (3.0 g, 20 mmol) and hydrated sodium *p*-toluenesulfinate (5.0 g) in a mixture of *N*,*N*-dimethylformamide (20 mL) and water (5 mL) was stirred at 50°C for 16 h, diluted with water (100 mL), and stirred at room temperature until the precipitated oil had solidified. The solid was collected by filtration and recrystallized from cyclohexane to give the *product* **11j** as white granular crystals (3.6 g, 67%), mp 85–86°C. (Found: C 57.8, H 7.4, N 5.3. $C_{13}H_{19}NO_3S$ requires C 58.0, H 7.1, N 5.2%). δ_H 1.04 (3H, t, *J* 7.3, NCH_2CH_3), 1.15 (3H, t, *J* 7.3, NCH_2CH_3), 2.38 (3H, s, $ArCH_3$), 3.27 (2H, q, *J* 7.3, NCH_2), 3.40 (2H, q, *J* 7.3, NCH_2), 4.15 (2H, s, $COCH_2$), 7.28 (2H, d, *J* 8.0, 2 × ArH), 7.72 (2H, d, *J* 8.4, 2 × ArH). δ_C 12.7, 14.2, 21.7, 40.7, 43.1, 59.8, 128.6, 129.6, 135.8, 145.1, 160.5. *m*/*z* (APCI) 270.3 $[M + H]^+$.

2-Diethylamino-3-(toluene-4-sulfonyl)thiochromen-4-one ***13j***

Phosphorus oxychloride, 2-mercaptobenzoic acid, and *N*,*N*-diethyl-2-(toluene-4-sulfonyl)acetamide were reacted in acetonitrile to give **13j**. Recrystallization from aqueous ethanol gave the *product* as colourless shiny crystals (53%), mp 180–181°C. (Found: C 61.8, H 5.7, N 3.7, S 16.3. $C_{20}H_{21}NO_3S_2$ requires C 62.0, H 5.5, N 3.6, S 16.6%). δ_H 1.38 (6H, t, *J* 7.3, $2NCH_2CH_3$), 2.32 (3H, s, $ArCH_3$), 3.91 (4H, q, *J* 7.3, $2NCH_2$), 7.12 (2H, d, *J* 8.0, 2ArH), 7.32–7.53 (3H, m, 3ArH), 7.74 (2H, d, *J* 8.4, 2ArH), 8.06 (1H, dd, *J* 1.5, 9.5, ArH). δ_C 13.3, 21.5, 50.1, 114.0, 125.3, 127.4, 127.9, 128.5, 128.6, 130.7, 131.5, 131.7, 140.7, 142.6, 164.9, 177.2. *m*/*z* (APCI) 388.2 $[M + H]^+$.

*1-Methyl-1,2,3,4-tetrahydrothiochromeno[2,3-*b*]pyridin-5-one* ***16a***

N-Methyl-2-piperidone (0.4 g, 3.5 mmol) in dichloromethane (2 mL) was added dropwise to a solution of phosphorus oxychloride (0.83 mL, 8.9 mmol) in dichloromethane (2 mL) at 0°C. The mixture was stirred at 0°C for 10 min, then at room temperature for 1 h. Then 2-mercaptobenzoic acid (0.61 g, 4.0 mmol) was added in one portion to the mixture and the resultant yellow suspension was stirred at room temperature for 3 days. The reaction mixture was poured into water (10 mL) and neutralized with solid potassium carbonate (1–2 g), followed by extraction with dichloromethane. The organic phase was washed with water, and concentrated under vacuum to form an oil phase that solidified upon standing. The crude thiochromene was purified by radial chromatography over silica (ethyl acetate/light petroleum, 1/9). Recrystallization from ethyl acetate gave light yellow *crystals* (0.34 g, 37%), mp 158–160°C. (Found: C 67.3, H 5.8, N 6.1, S 14.0. $C_{13}H_{13}NOS$ requires C 67.5, H 5.7, N 6.1, S 13.9%). δ_H 1.99 (2H, m, $CH_2CH_2CH_2$), 2.84 (2H, m, $CH_2CH_2CH_2N$), 3.20 (3H, s, Me), 3.44 (2H, m, $CH_2CH_2CH_2N$), 7.45 (3H, m, 3 × ArH), 8.54 (1H, m, ArH), δ_C 20.8 (C3), 21.6 (C4), 39.5 (C2), 52.2 (NCH_3), 107.7 (C8), 125.1 (C9), 126.7 (C8), 128.4 (C6), 129.4 (C9a), 129.6 (C7), 131.5 (C5a), 155.1 (C10a), 176.2 (C5). *m*/*z* (APCI) 232.1 $[M + H]^+$.

*1-Propyl-1,2,3,4-tetrahydrothiochromeno[2,3-*b*]pyridin-5-one* ***16b***

The reaction between *N*-propyl-2-piperidone (0.5 g, 3.5 mmol), phosphorus oxychloride (0.83 mL, 8.90 mmol), and 2-mercaptobenzoic acid (0.61 g, 4.0 mmol) gave the crude thiochromene which was purified by radial chromatography over silica (ethyl acetate/light petroleum, 1/9) to give a yellow solid (0.63 g, 69%), mp 106–108°C. Recrystallization from benzene/cyclohexane gave pale yellow *needles*, mp 107–108°C. (Found: C 69.5, H 6.7, N 5.5, S 12.1. $C_{15}H_{17}NOS$ requires C 69.5, H 6.6, N 5.4, S 12.4%). δ_H 0.96 (3H, t, *J* 7.3, Me), 1.67 (4H, m), 1.91 (4H, m), 2.75 (2H, m), 3.37 (3H, m), 7.38 (3H, m, 3ArH), 8.41 (H, m, ArH). δ_C 11.2, 20.7, 20.9, 22.1, 50.3, 54.2, 107.5, 125.2, 126.7, 128.4, 129.5, 129.7, 131.5, 154.2, 176.8. *m*/*z* (APCI) 260.3 $[M + H]^+$.

*8-Chloro-1-ethyl-1,2,3,4-tetrahydrothiochromeno[2,3-*b*]pyridin-5-one* ***16c***

In a similar manner to **16b**, **16c** was prepared using 4-chloro-2-mercaptobenzoic acid (0.82 g, 4.3 mmol), phosphorus oxychloride (0.92 mL, 9.8 mmol), and *N*-ethyl-2-piperidone (0.5 g, 3.9 mmol). The product **16c** was obtained (0.23 g, 21%) as yellow *prisms* after recrystallization from ethyl acetate, mp 177–179°C. (Found: C 59.9, H 5.0, N 5.1, S 11.3. $C_{14}H_{14}ClNOS$ requires C 60.1, H 5.0, Cl 12.7, N 5.0, S 11.5%). δ_H 1.26 (3H, t, *J* 6.9, Me), 1.93 (2H, m, $CH_2CH_2CH_2$), 2.73 (2H, m, $NCH_2CH_2CH_2$), 3.36 (2H, m, $NCH_2CH_2CH_2$), 3.50 (q, *J* 6.9, CH_2Me), 7.32 (2H, m, 2 × ArH), 8.34 (1H, d, *J* 8.8, ArH). δ_C 12.2, 20.7, 21.9, 47.3, 49.6, 107.6, 124.4, 127.3, 127.7, 130.0, 132.8, 135.9, 153.7, 175.5. *m*/*z* (APCI) 280.1, 282.1 $[M + H]^+$.

*8-Chloro-1-(2-chlorobenzyl)-1,2,3,4-tetrahydrothiochromeno-[2,3-*b*]pyridin-5-one* ***16d***

This compound was prepared similarly from 4-chloro-2-mercaptobenzoic acid (0.5 g, 2.6 mmol), phosphorus oxychloride (0.62 mL, 6.6 mmol), and 1-(2-chloro-benzyl)piperidin-2-one (0.6 g, 2.64 mmol). The product (0.26 g, 26%) formed *yellow needles* after recrystallization from ethyl acetate, mp 197–199°C. (Found: C 60.4, H 4.0, N 3.7, S 8.5. $C_{19}H_{15}Cl_2NOS$ requires C 60.6, H 4.0, Cl 18.8, N 3.7, S 8.5%). δ_H 2.04 (2H, m, $CH_2CH_2CH_2$), 2.90 (2H, m, $CH_2CH_2CH_2N$), 3.47 (2H, m, *J* 5.8, $CH_2CH_2CH_2N$), 4.81 (2H, s, CH_2Ph), 7.28–7.48 (m, 6 × ArH), 8.43 (1H, d, *J* 9.1, ArH). δ_C 20.7, 22.0, 51.0, 53.9, 108.6, 124.6, 127.0, 127.2, 127.4, 127.7, 129.3, 130.1, 130.2, 132.3, 132.7, 133.2, 136.5, 155.3, 175.3. *m*/*z* (APCI) 375.9, 378.0 $[M + H]^+$.

*1-Methyl-1,2,3,4-tetrahydrothiochromeno[2,3-*b*]pyridin-5-one* ***16e***

Preparation by the standard method from 2-mercaptobenzoic acid, *N*-methylcaprolactam, and phosphorus oxychloride followed by recrystallization from cyclohexane gave **16e** as colourless *crystals* (28%), mp 79–80°C. (Found: C 68.3, H 6.2, N 5.7, S 13.1. $C_{14}H_{15}NOS$ requires C 68.5, H 6.2, N 5.7, S 13.1%). δ_H 1.82 (4H, m, $CH_2CH_2CH_2CH_2$), 2.94 (2H, m, $CH_2CH_2CH_2CH_2N$), 3.12 (3H, s, Me), 3.41 (2H, m, CH_2N), 7.44 (3H, m, 3ArH), 8.45 (1H, m, ArH). δ_C 23.1, 26.0, 26.1, 40.5, 55.0, 56.7, 117.7, 125.4, 126.7, 128.7, 130.1, 132.9, 159.4, 179.6. *m*/*z* (APCI) 246.1 $[M + H]^+$.

*6-(4-Chlorobenzyl)-7,8,9,10-tetrahydro-6*H*-5-thia-6-azacyclohepta[*b*]naphthalen-11-one* ***16f***

In a similar manner, **16f** was prepared from 2-mercaptobenzoic acid (0.4 g, 2.52 mmol), phosphorus oxychloride (0.5 mL, 5.3 mmol), and *N*-(4-chlorobenzyl) caprolactam (0.5 g, 2.1 mmol). The crude product (0.11 g, 15%) gave light-yellow oil after chromatography (ethyl acetate/light petroleum, 1/9) that gradually solidified. Recrystallization from cyclohexane gave **16f** as a colourless *solid*, mp 228–230°C. (Found: C 67.4, H 5.0, Cl 10.1, N 3.8. $C_{20}H_{18}ClNOS$ requires C 67.5,

H 5.1, Cl 10.0, N 3.9%). δ_H 1.77 (4H, m, $CH_2CH_2CH_2CH_2$), 3.00 (2H, m, $CH_2CH_2CH_2CH_2N$), 3.37 (2H, m, $CH_2CH_2CH_2CH_2N$), 4.62 (2H, s, CH_2Ph), 7.28–7.40 (4H, m, CH_2Ph), 7.40–7.51 (3H, m, 3ArH), 8.47 (1H, m, ArH). δ_C 23.6, 26.5, 53.5, 56.6, 120.3, 125.8, 127.2, 129.1, 129.2, 129.3, 129.6, 130.0, 130.8, 133.4, 133.9, 135.8, 159.0, 180.7. *m/z* (APCI) 356.1, 358.0 $[M + H]^+$.

1-Benzyl-1,2,3,4-tetrahydro-9-thia-1,8-diazaanthracen-10-one ***16g***

Phosphorus oxychloride (3.1 g, 20 mmol) was added to chilled 1-benzyl-2-piperidone (1.9 g, 10 mmol) and the mixture was left at room temperature overnight. The next day, 2-mercaptonicotinic acid (1.0 g, 6.7 mmol) was stirred into the mixture, and after 3 h the mixture was added to ice (60 g) and ethyl acetate (40 mL). Sodium carbonate was added in portions to pH 9, the organic phase separated, washed with water (20 mL), and evaporated. The residue was chromatographed over silica gel using dichloromethane and then dichloromethane containing 5, 10, and 15% ethyl acetate. The later fractions containing a spot with pale blue fluorescence (silica TLC plates eluted with 10% ethyl acetate/dichloromethane and visualized using 254 nm wavelength illumination) were combined, the solvent was evaporated, and the residue recrystallized from isopropyl alcohol to give the *product* **16g** (0.58 g, 29%). A portion was recrystallized from isopropanol giving colourless needles, mp 152–154°C. (Found: C 70.05, H 5.4, N 9.0, S 10.2. $C_{18}H_{16}N_2O_2S$ requires C 70.1, H 5.2, N 9.1, S 10.4%). δ_H 1.94–2.02 (2H, m, $CH_2CH_2CH_2$), 2.82 (2H, t, *J* 6.2, $NCH_2CH_2CH_2$), 3.41–3.47 (2H, m, NCH_2), 4.75 (2H, s, $ArCH_2$), 7.27–7.46 (6H, m, ArH and pyH), 8.56–8.61 (1H, m, pyH), 8.67–8.71 (1H, m, pyH). δ_C 20.6, 22.0, 50.6, 55.8, 108.0, 122.3, 126.5, 127.0, 128.0, 129.0, 135.3, 136.3, 150.9, 153.7, 155.5, 176.7. *m/z* (APCI) 309.0 $[M + H]^+$.

1-Benzyl-1,2,3,4-tetrahydro-9-thia-1,8-diazaanthracene-10-thione ***16h***

Phosphorus oxychloride (4.6 g, 30 mmol) was added to a mixture of 2-mercaptonicotinic acid (1.6 g, 10 mmol) and 2-benzyl piperidone (1.9 g, 10 mmol) in sulfolane (10 mL), and stirred overnight. It was then added to ice water (100 mL) and dichloromethane (50 mL), and brought to pH 7 by portion-wise addition of solid sodium carbonate. The organic phase was separated, washed with water (100 mL), then allowed to partially evaporate (to ~25 mL). The red crystals (0.17 g) were filtered off and washed with benzene. A further quantity was obtained by chromatography of the combined filtrate over silica gel with elution by dichloromethane. Combined yield of *product* **16h** 0.45 g (14%), mp 214–216°C. (Found: C 66.5, H 5.0, N 8.6, S 19.6. $C_{18}H_{16}N_2S_2$ requires C 66.6, H 5.0, N 8.6, S 19.8%). δ_H [$(CD_3)_2SO$], 2.48–2.51 (2H, m, $CH_2CH_2CH_2$), 3.09 (2H, t, *J* 6.4, $NCH_2CH_2CH_2$), 3.62–3.67 (2H, m, NCH_2), 4.97 (2H, s, Ar CH_2), 7.30–7.43 (5H, m, ArH), 7.52–7.56 (1H, m, pyH), 8.61–8.63 (1H, m, pyH), 9.21–9.25 (1H, m, pyH). δ_C [$(CD_3)_2SO$] 20.5, 29.3, 51.7, 56.3, 122.2, 123.0, 126.7, 127.8, 129.0, 129.6, 134.5, 140.4, 148.6, 150.4, 156.4, 188.5. *m/z* (APCI) 325.0 $[M + H]^+$.

A similar experiment using 1,4-dioxan as solvent afforded the same compound in low yield (0.13 g, 4%).

Acknowledgments

Thanks to Mr Tony Wilson for technical assistance, to Dr Gary Fallon for verification of the structure of **16h** by X-ray analysis, and to DuPont Agricultural Products (Stine–Haskell, Delaware) for biological screening.

References

[1] C. A. Lipinski, *J. Pharmacol. Toxicol. Meth.* **2000**, *44*, 235. doi:10.1016/S1056-8719(00)00107-6

[2] P. Kumar, M. S. Bodas, *Tetrahedron* **2001**, *57*, 9755. doi:10.1016/S0040-4020(01)00977-2

[3] G. Eiden, H. Felbermeir, H. Buchborn, *Arch. Pharm. (Weinheim)* **1983**, *316*, 921.

[4] D. R. Tatke, S. Seshadri, A. Das, R. R. M. Rao, *Ind. J. Chem. B* **1979**, *17*, 491.

[5] C. Hansch, B. Schmidhalter, *J. Org. Chem.* **1955**, *20*, 1056. doi:10.1021/JO01365A016

[6] S. Lin, B. Moon, K. T. Porter, C. A. Rossman, T. Zennie, J. Wemple, *Org. Prep. Proced. Int.* **2000**, *36*, 547.

[7] A. L. Cossey, R. L. N. Harris, J. L. Huppatz, J. N. Phillips, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 1098. doi:10.1002/ANIE.197210981

[8] H. Schultze, E. Schlumbohm, E. Sommermeyer, *Chem. Ber.* **1925**, *58*, 1654.

[9] L. Katz, L. S. Karger, W. Schroeder, M. S. Cohen, *J. Org. Chem.* **1953**, *18*, 1380. doi:10.1021/JO50016A019