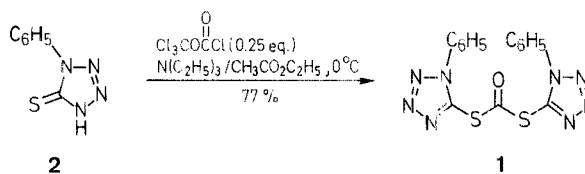


mediate which is formed from the carboxylic acid (or a derivative thereof) and the coupling reagent and which undergoes nucleophilic attack by the hydroxy group of an alcohol.

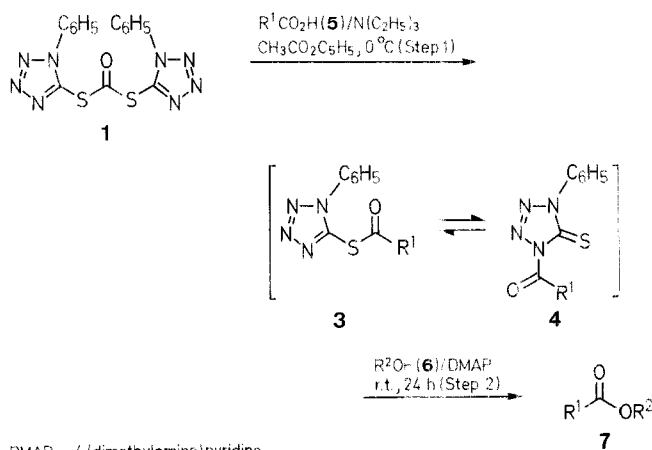
We have earlier reported² that bis[6-(trifluoromethyl)benzotriazol-1-yl] oxalate is a versatile coupling reagent which can be used for the preparation of carboxylic esters and thiocarboxylic esters and for peptide formation. As an extension of our work in this field we now report the preparation and use as coupling reagent of *S,S'*-bis(1-phenyl-1*H*-tetrazol-5-yl) dithiocarbonate (**1**). Reagent **1** is easily prepared in 77% yield by reaction of 1-phenyl-5-thioxo-4,5-dihydro-1*H*-tetrazole³ (**2**) with trichloromethyl chloroformate (trichloromethyl carbonochloridate) and triethylamine in ethyl acetate at 0 °C.



The crystalline reagent **1** is stable enough to be stored in a desiccator at room temperature for a period of at least three months.

The structure of reagent **1** was confirmed by single-crystal X-ray analysis (Figure) and by ¹³C-NMR spectrometry. The ¹³C-NMR signals of the carbonyl group and of C-5 in the tetrazole rings were observed at $\delta = 176.56_{\text{s}}$ and 143.84_{s} ppm, respectively.

The conversion of carboxylic acids (**5**) into esters (**4**) using reagent **1** was carried out by a one-pot procedure at room temperature in the presence of triethylamine, using a slight excess of the alcohol **6**, and of reagent **1**. The procedure consists of two reactions: initial formation of reactive intermediates (**3** or **4**) from the carboxylic acids (**5**) (step 1), and alcoholysis of the intermediate (**3** or **4**) (step 2). Alcoholysis requires the presence of 2 equivalents of 4-dimethylaminopyridine (DMAP) in step 2.



DMAP = 4 (dimethylamino)pyridine

S,S'-Bis(1-phenyl-1*H*-tetrazol-5-yl) Dithiocarbonate: A New Esterification Reagent

Kazuyoshi Takeda, Kanoko Tsuboyama, Hiroaki Takayanagi, Haruo Ogura*


School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108, Japan

S,S'-Bis(1-phenyl-1*H*-tetrazol-5-yl) dithiocarbonate is a useful reagent for the esterification of carboxylic acids with alcohols, including lactonization. The reagent is conveniently prepared in good yield from 1-phenyl-5-thioxo-4,5-dihydro-1*H*-tetrazole and trichloromethyl chloroformate (trichloromethyl carbonochloridate) in ethyl acetate in the presence of triethylamine. Its structure was confirmed by ¹³C-NMR spectrometry and single-crystal X-ray analysis.

The use of coupling reagents for the convenient preparation of carboxylic esters and lactones is the subject of many publications.¹ The coupling reactions leading to esters or lactones usually involve an activated carboxylic acid derivative as inter-

In order to confirm the reaction pathway, reagent **1** was submitted to the reaction with benzoic acid (**5a**) in the presence of triethylamine in ethyl acetate at 0 °C (30 min). Intermediates **3** or **4**, were thus obtained together with a small amount of benzoic anhydride. Formation of the anhydride could be completely suppressed by the addition of an equivalent amount of compound **2**, the desired reactive intermediate (**3** or **4**) being obtained in good yield.

Table. Preparation of Carboxylic Esters (**7**) using Reagent **1** in the Presence of DMAP

Ester 7	Carboxylic Acid 5 : R ¹ (0.5 mmol)	Alcohol 6 : R ² (mmol)	Yield ^d (%)	Molecular Formula	MS (70 eV) <i>m/z</i> (M ⁺)	IR (film) $\nu_{C=O}$ (cm ⁻¹)	¹ H-NMR (CDCl ₃) δ (ppm)
a	C ₆ H ₅	C ₂ H ₅	85	C ₉ H ₁₀ O ₂ ^a (150.2)	150	1725	
b	C ₆ H ₅	 (0.55)	85	C ₁₂ H ₁₀ O ₃ ^b (202.2)	202	1720	4.22 (s, 2H); 6.14–6.45 (m, 2H); 7.30–8.08 (m, 6H)
c	C ₆ H ₅	H ₂ C=C(CH ₃)CH ₂ (0.55)	97	C ₁₁ H ₁₂ O ₂ ^b (176.2)	176	1730	1.82 (s, 3H); 4.73 (s, 2H); 5.01 (br d, 2H, <i>J</i> = 6 Hz); 7.32–8.21 (m, 5H)
d	C ₆ H ₅	<i>i</i> -C ₃ H ₇ (0.55)	83	C ₁₀ H ₁₂ O ₂ ^b (164.2)	164	1700	1.30 (s, 3H); 1.41 (s, 3H); 5.01–5.40 (m, 1H); 7.28–8.14 (m, 5H)
e	CH ₃	geranyl (0.55)	53	C ₁₂ H ₂₀ O ₂ ^a (196.3)	196	1750	
f	C ₂ H ₅	C ₆ H ₅ CH=CHCH ₂ (0.55)	97	C ₁₂ H ₁₄ O ₂ ^b (190.2)	190	1730	1.15 (t, 3H, <i>J</i> = 8 Hz); 2.35 (q, 2H, <i>J</i> = 8 Hz); 4.68 (d, 2H, <i>J</i> = 4.4 Hz); 5.92–6.76 (m, 2H); 7.08–7.55 (m, 5H)
g	C ₆ H ₅ CH ₂	C ₂ H ₅ (0.6)	85	C ₁₀ H ₁₂ O ₂ ^a (164.2)	164	1710	
h	C ₆ H ₅ CH ₂	H ₂ C=CHCH ₂ (0.55)	90	C ₁₁ H ₁₂ O ₂ ^b (176.2)	176	1720	3.05 (s, 2H); 4.57 (d, 2H, <i>J</i> = 5.6 Hz); 5.10–5.42 (m, 2H); 5.61–6.19 (m, 1H); 7.28 (s, 5H)
i	C ₆ H ₅ CH ₂	CCl ₃ CH ₂ (0.55)	67	C ₁₀ H ₉ Cl ₃ O ₂ ^b (267.5)	267, 268	1750	3.72 (s, 2H); 4.70 (s, 2H); 7.25 (s, 5H)
j	C ₆ H ₅ CH=CH	C ₂ H ₅ (0.55)	84	C ₁₁ H ₁₂ O ₂ ^b (176.2)	176	1710	1.50 (t, 3H, <i>J</i> = 6.4 Hz); 4.35 (q, 2H, <i>J</i> = 6.4 Hz); 6.48 (d, 1H, <i>J</i> = 15 Hz); 7.20–7.54 (m, 5H); 7.70 (d, 1H, <i>J</i> = 15 Hz)
q ^c	16-hydroxy-hexadecanoic acid	(0.5)	54	C ₁₆ H ₃₀ O ₂ ^b (254.4)	254	1725	1.05–1.91 (m, 26H); 2.04–2.45 (m, 2H); 3.91–4.17 (m, 2H)

^a These compounds were identified by IR and TLC comparison with authentic samples which were supplied by Tokyo Kasei Co.

^b The microanalyses were in satisfactory agreement with the calculated values: C \pm 0.30, H \pm 0.29.

^c The reaction was carried out in refluxing toluene in the presence of triethylamine.

^d All compounds were oils, except for **7q**: m.p. = 33–34.5°C.

The active intermediates **3** or **4** having acetyl groups, obtained from compound **2**, *t*-butyl isocyanide, and a carboxylic acid (**5**),⁴ have been reported to be a mixture of the tautomeric structures **3** and **4** in the ratio 7:5 according to ¹H-NMR analysis.⁴

To demonstrate the utility of the new reagent **1**, the synthesis of macrolide **7q** was carried out using equivalent amounts of reagent **1** and triethylamine in refluxing toluene; lactone **7q** was thus obtained in 54% yield.

The new condensing agent **1**, is a crystalline solid having high stability against humidity; it can therefore be handled more easily than conventional condensing agents such as dicyclohexylcarbodiimide (DCC).

One of the merits of our procedure is that it works well even in basic media, whereas the most frequently used DCC-based activation of carboxylic acid does not work well in basic media. In addition, our present method affords high yields, the reaction is fast, mild conditions are used, and work-up is simple.

S,S'-Bis(1-phenyl-1*H*-tetrazol-5-yl) Dithiocarbonate (**1**):

A mixture of 1-phenyl-5-thioxo-4,5-dihydro-1*H*-tetrazole (**2**; 5.3 g, 30 mmol) and triethylamine (3.1 g, 30 mmol) in ethyl acetate (200 ml) is stirred at

0°C and a solution of trichloromethyl chloroformate (0.9 ml, 7.5 mmol) in ethyl acetate (50 ml) is added dropwise. Stirring is continued for 6 h and the precipitate is then filtered off. The filtrate is evaporated and the residue crystallized from ethyl acetate/ether; yield: 4.6 g (77%); m.p. 126°C (dec.).

C₁₅H₁₀N₈OS₂ calc. C 47.11 H 2.63 N 29.30
(382.3) found 46.94 2.66 29.14

MS: *m/z* = 382 (M⁺).

IR (KBr): ν = 1720 (C=O) cm⁻¹.

¹H-NMR (CDCl₃): δ = 7.32–8.14 (m, 10H, 2 C₆H₅).

Carboxylic Esters (7); General Procedure:

Reagent **1** (199 mg, 0.52 mmol) is added to an ice-cooled, stirred solution of the carboxylic acid (**5**; 0.5 mmol) and triethylamine (61 mg, 0.6 mmol) in ethyl acetate (15 ml). After 30 min, the alcohol **6**: (0.55–0.65 mmol) and 4-dimethylaminopyridine (122.2 mg, 1 mmol) are added. Stirring is continued for 24 h at room temperature. The mixture is evaporated and the residue is extracted with chloroform (3 \times 50 ml). The organic layer is successively washed with 4% sodium hydrogen carbonate solution, (80 ml), 1 normal hydrochloric acid (80 ml), and is saturated sodium chloride solution (80 ml), and dried with sodium sulfate. The solvent is removed under reduced pressure, and the residue is subjected to TLC on silica gel to afford the ester **7**.

16-Hexadecanolide (7q):

A mixture of reagent **1** (199 mg, 0.52 mmol), 16-hydroxyhexadecanoic acid (136 mg, 0.5 mmol), and triethylamine (61 mg, 0.6 mmol) in dry toluene (100 ml) is refluxed for 2 h. The mixture is worked up as described above; yield: 68.7 mg (54%), m.p. 33–34.5°C.

Received: 6 August 1986

(Revised form: 22 January 1987)

(1) For general reviews, see:

Ogliaruso, M.A., Wolfe, J.F., in: *The Chemistry of Acid Derivatives*, Patai, S. (ed.), John Wiley & Sons, New York, 1979, Part I.

Bodanszky, M., Hausner, Y.S., Ondetti, M.A., in: *Peptide Synthesis*, John Wiley & Sons, New York, 1976.

Bodanszky, M., in: *The Peptides*, Gross, E., Meienhofer, J. (eds.), Vol. I, Academic Press, New York, 1979, p. 105.

Haslam, H. *Tetrahedron* **1980**, *36*, 2409.

(2) Takeda, K., Tsuboyama, K., Yamaguchi, K., Ogura, H. *J. Org. Chem.* **1985**, *50*, 273.

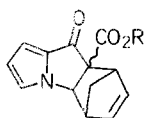
(3) Lieber, E., Ranachermdran, J. *Can. J. Chem.* **1959**, 101.

(4) Schmidt, U., M. Dietshe, M. *Angew. Chem.* **1981**, *93*, 786; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 771.

Errata and Addenda 1987

Hall, G., Sugden, J. K., Waghela, M. B.

Page 10. Line 3 of the Abstract should read: dropyrolizines ...
Page 14. The first word of Section 3.11. should be: Benzo[*b*]pyrroli-
zines.
Page 15. Formula 27 should be:

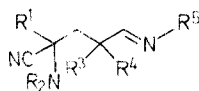


27

Page 15. The product referred to in Section 4.6., lines 4-5, should be:
10*H*-pyrrolizino[1,2-*b*]quinoline
Page 17. In Section 7., line 4 of the second paragraph should read:
34.¹⁸² ...

Ahnbrecht, H., von Daacke, A.

Page 24. Formula 8 should be:



8

Costisella, B., Keitel, I.

Page 45. In the heading of the experimental procedure, 6 should read 3
and 8 should read 7.

Stoss, P., Merrath, P., Schlüter, G.

Page 174. Numbers 1 and 3 should be exchanged in formula 2a-f.

Singh, G., Deb, B., Ila, H., Junjappa, H.

Page 286. Compounds 1 are 2-aryl-2-arylthio ketene dithioacetals.

Asaad, F. M., Becher, J., Möller, J., Varma, K. S.

Page 301. Under the reaction scheme, the X group in compounds 3b,d
and 4b,d should be CO₂C₂H₅.

Legrel, P., Baudy-Floc'h, M., Robert, A.

Page 306. The title should read: A One-Pot Synthesis of α -Halohydrazides
from 2,2-Dicyano oxiranes.

Page 306. In the table under the reaction scheme, the second heading R¹
should be R².

van der Goorbergh, J. A. M., van der Steeg, M., van der Gen, A.

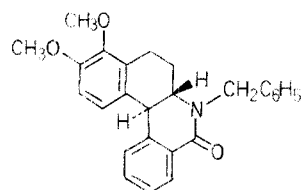
Pages 314-317. The systematic names for the heterocycles involved are:
4,5-dioxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzopyrans 4 (RF
24756), 4,5-dioxo-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzopyrans 7 (RF
24756j), and 4,5-dioxo-1,3,4,4a,5,10b-hexahydro-2*H*-[1]benzopy-
rano[4,3-*b*]pyridines 8 (RF 24539).

Attanasi, O. A., Filippone, P., Santensanio, S., Serra-Zanetti, F.

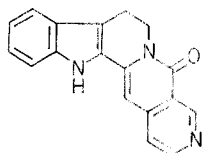
Page 382. In the table under the reaction scheme, R³ for 1b should be
CO₂C₂H₅ and R³ for 1c should be CO₂CH₃.

Campbell, A. I., Lenz, G. R.

Pages 428 and 446. Formulae 95 and 298 should be:



95

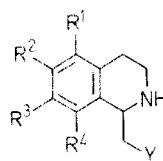


298

Page 437. The heading for Table 3 should be: Intermolecular ...

Pelletier, J. C., Cava, M. P.

Page 476. Formula 1a-m should be:



1a-m

L'abbé, G.

Page 528. Compound 45 should be named: 3-(2-pyridyl)-2,4-dithio-
3,4-dihydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine (RF 9177).

Evans, R. D., Schauble, J. H.

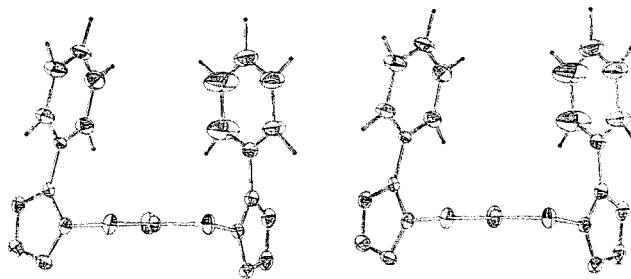
Page 551. Compounds 10 and 11 are tricyclo[2.2.1.0^{2,6}]heptane deriva-
tives.

Takeda, K., Tsuboyama, K., Hoshino, M., Kishino, M., Ogura, H.

Page 559. The Y-group for 2g and 2j should be furfuryloxy.

Takeda, K., Tsuboyama, K., Takayanagi, H., Ogura, H.

Page 560. The following figure should appear after the 4th paragraph:

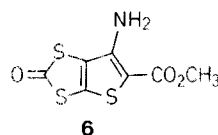


Eicher, T., Stapperfenne, U.

Page 625. Compounds 13a,b are 6,7-dihydrofuro[2,3-*b*]pyridines
(RF 7431), and compounds 15a,b are 1,4-dihydrocyclopentimidazoles
(RF 5892).

Dölling, W., Augustin, M., Ihrke, R.

Page 655. Formula 6 should be:



6

Mikolajczyk, M., Balczewski, P.

Page 661. The second paragraph of ref. 21 should be ref. 22; refs. 22 and
23 should be 23 and 24, respectively.

Rösch, W., Regitz, M.

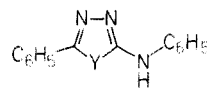
Page 692. Compounds 21a,b are 2*H*-1,2,3-diazaphospholes.

Tietze, L.-F., Brumby, T., Pretor, M.

Page 702. Compounds 8 and 9 are 4a,10b-dihydro-4*H*,5*H*-pyrano[3,4-
c][1]benzopyran-2-carboxylic esters.

Wamhoff, H., Zahran, M.

Page 877. Formula 18a,b should be:



18a,b

Castaldi, G., Giordano, C.

Page 1039. The target compounds 3 are 1-bromoalkyl aryl ketones.