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SYNTHESIS OF PHENACYL ESTERS VIA AN ORGANOTIN ROUTE

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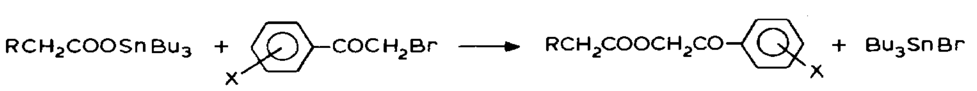
Summary

A facile and convenient method for the synthesis of phenacyl esters using organostannyl carboxylates and phenacyl bromides in the presence of quaternary ammonium salts is reported. In the absence of the quaternary ammonium salt the yields are poor and the reaction is incomplete.

Introduction

In studies aimed at extending the synthetic applications of bis(tri-n-butyl)tin oxide (TBTO) (a commercially available fungicide) [1,2], we have shown that it can be used for the synthesis of phenacyl esters. Phenacyl esters are potential precursors for the synthesis of certain biologically active lactones [3], and there are also several reports on the utility of phenacyl esters as protecting groups in peptide synthesis. The traditional method of preparing phenacyl esters [4] has certain disadvantages, such as (i) slow reaction times, (ii) hydrolysis of the alkylating agent, (iii) low yields of product, and (iv) contamination of products with the starting alkylating agent. Some of these difficulties can be overcome by use of crown ethers [5]. The method we have now developed for the synthesis of such esters involves the reaction of trialkylstannyl carboxylates with the phenacyl bromides:

$$2\ RCH_2COOH + (Bu_3Sn)_2O \xrightarrow{\text{benzene}} 2\ RCH_2COOSnBu_3 + H_2O \qquad (1)$$



(2)

Results and discussion

As a representative of the series, the preparation of *p*-bromophenacyl phenylacetate was investigated. A solution of the tri-n-butylstannyl phenylacetate and the

TABLE 1

PREPARATION OF *p*-BROMOPHENACYL PHENYLACETATE FROM TRI-n-BUTYLSTANNYLPHENYL ACETATE IN VARIOUS SOLVENTS

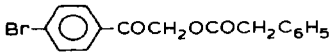
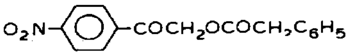
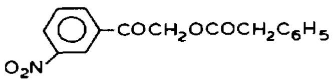
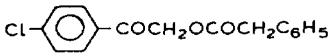
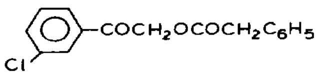
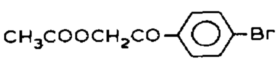
Solvent	Yield [a] (%)
Acetone	60
Acetonitrile	50
Ethanol	50
Diethyl ether	5
Benzene	2.5
Hexane	Trace
Carbontetrachloride	Trace

[a] Isolated yields.

p-bromophenacyl bromide in acetone was refluxed for 6 h, and the tin species were removed as insoluble tri-n-butyltin fluoride [6]. The product was then purified by column chromotography on silica gel with benzene as eluant. The yield of the phenacyl ester was only 45% when equimolar amounts of the reagents were used, but

TABLE 2

PREPARATION OF PHENACYL ESTERS FROM TRI-n-BUTYLSTANNYL CARBOXYLATES AND VARIOUS PHENACYL BROMIDES IN ACETONE

Ester	M.p. [b] (°C)	Yield [a] (%)
	88 (89)	60
	86	54
	44–45	38
	85–86	17
	48–50	30
	88 (88.2–88.8)	27
$C_6H_5COCH_2OCOCH_2C_6H_5$	50 (50)	20
	83–85 (85)	40

[a] Isolated yields. [b] Literature m.p. in parentheses.

with an excess of the tri-n-butylstannyl carboxylate the yield increased to 60%. Increasing the reaction time from 6 to 24 h caused no significant change in the yield. Various other solvents were tried, with the results summarised in Table 1. The method was extended to the preparation of other phenacyl esters in acetone, and the results are given in Table 2.

In addition to the low yields of the product and incomplete reaction even after prolonged reaction, the products were contaminated with a minor product, which constituted around 10% by weight. This minor product was found to be the same irrespective of the phenacyl bromide employed, and it had the same characteristics as the product formed when tri-n-butylstannyl phenylacetate was refluxed with tri-n-butyltin bromide in acetone for 6 h. [The details are: m.p. 57–58°C, IR (KBr) ν (cm^{-1}): 2980–2960, 1580–1560, 1380–1360. UV (EtOH): λ_{max} (nm): 260, 270, 286; ^1H NMR (CCl_4/TMS): δ 0.5–1.8 (m, 18H); 3.5 (s, 2H) and 7.2 ppm (s, 5H) MS m/e (%): 369 (4.6), 368 (2), 367 (3.5), 177 (10), 175 (7), 137 (10.4), 136 (19.6), 135 (8.7), 121 (9.3), 120 (5.4), 119 (8.5), 117 (5), 92 (16), 91 (100), 65 (25), 57 (24). The product is under investigation.]

The difficulties were overcome when the reaction was carried out in the presence of quaternary ammonium salts such as tetra-n-butylammonium bromide, benzyltriethylammonium chloride, or Triton B. When the organostannylcarboxylate was refluxed with phenacyl bromide in acetonitrile in presence of the quaternary ammonium salt the ester formation complete within 1 h, and the side-product was absent. The yields of the phenacyl esters prepared by this procedure are listed in Table 3.

The main advantages of this method are: (i) mild and neutral conditions, (ii) use of an inexpensive reagent (TBTO), (iii) good yields, and (iv) recyclability of the tin reagent as the tri-n-butyltin halide.

Experimental

General

The solvents used were purified by standard methods and distilled before use. The melting points reported are uncorrected. The spectral data for the new phenacyl esters are given in Table 4. The phenacyl bromides and the phenacyl esters were recrystallised from hexane. Infrared spectra were recorded on a Perkin–Elmer 298 Infrared spectrophotometer. The UV spectra were recorded on a Hitachi 220A UV-visible spectrophotometer. The PMR spectra were recorded on a Varian EM 360 60 MHz spectrophotometer. The mass spectral data were obtained with a Finnigan 4000 GC-MS Spectrometer.

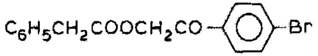
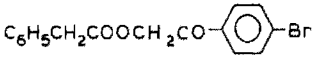
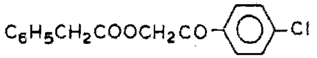
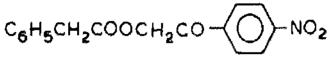
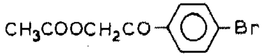
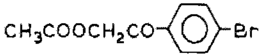
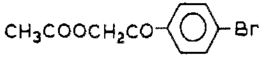
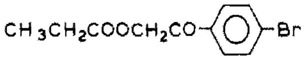
Preparation of tri-n-butylstannyl phenylacetate

A mixture of phenylacetic acid (6.8 g, 50 mmol) and TBTO (14.9 g, 25 mmol) in dry benzene was refluxed for 3 h, the water formed being removed as an azeotrope using a Dean-Stark apparatus. The solvent was removed with a rotary evaporator and the product was recrystallised from 75% ethanol. Yield, 16.4 g (77%), m.p. 60–62°C (lit. [7] 61–62°C). IR ν(CO) (cm^{-1}) (KBr): 1560, 1390; (CCl_4): 1650, 1350, 1320.

(Continued on p. 22)

TABLE 3

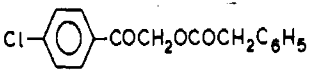
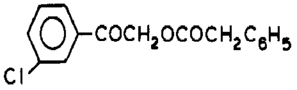
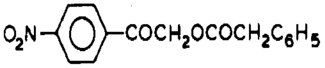
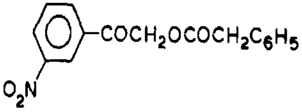
PREPARATION OF PHENACYL ESTERS FROM ORGANOSTANNYL CARBOXYLATES AND PHENACYL BROMIDES USING QUATERNARY AMMONIUM SALTS

Organostannyl ester	Product	Quaternary ammonium salt	Yield[a] (%)	M.p. (°C)
$C_6H_5CH_2COOSnBu_3$		$(C_4H_9)_4NBr$	66	88–89
$C_6H_5CH_2COOSnBu_3$		$C_6H_5CH_2N(C_2H_5)_3Cl$	72	88–89
$C_6H_5CH_2COOSnBu_3$		$C_6H_5CH_2N(C_2H_5)_3Cl$	74	85–86
$C_6H_5CH_2COOSnBu_3$		$C_6H_5CH_2N(C_2H_5)_3Cl$	80	85–87
$CH_3COOSnBu_3$		$(C_4H_9)_4NBr$	70	84–85
$CH_3COOSnBu_3$		Triton B	55	80–83
$CH_3COOSnBu_3$		$C_6H_5CH_2N(C_2H_5)_3Cl$	71	84–85
$CH_3CH_2COOSnBu_3$		$C_6H_5CH_2N(C_2H_5)_3Cl$	50	57–59 (59)[b]

[a] Isolated after recrystallisation. [b] Lit. m.p.

TABLE 4

SPECTRAL DATA FOR NEW PHENACYL ESTERS

Ester	IR ν(CO) (cm^{-1})	UV (in CH_3CN) λ_{max} (nm) (ε)	^1H NMR (δ (ppm))	MS (m/e)
	(KBr), 1740, 1690	211.6 (13602); 252 (15690)	($CDCl_3$/TMS) 8.3–7 (m, 9H); 5.2 (s, 2H); 3.76 (s, 2H).	288, 290 (M^+), 141, 139, 118(base) 91.
	(CCl_4), 1750, 1715, 1640	212.5 (28076); 242 (12586)	(CCl_4/TMS) 7.8–6.9 (m, 9H); 5.0 (s, 2H); 3.56 (s, 2H);	290, 288.1 (M^+), 199, 197, 172, 170, 152, 141, 139, 119, 118 (base), 91.
	(KBr), 1690, 1600. 1350, 1530 (NO_2)	211 (8714); 263 (12042),	($CDCl_3$/TMS) 8.4–7.8 (m, 4H); 7.3 (s, 5H); 5.26 (s, 2H); 3.77 (s, 2H)	299.1 (M^+) 253 ($M-NO_2$)$^+$, 208, 181.1, 150, 118 (base), 91.1
	(CCl_4), 1755, 1720. 1530, 1355 (NO_2)	227 (20880)	(CCl_4/TMS) 8.6–8.7 (m, 9H); 5.18 (s, 2H); 3.26 (s, 2H).	299.1 (M^+), 165, 150, 134, 118, 91 (base), 76, 65.

Preparation of phenacyl bromides

The phenacyl bromides were prepared by direct bromination of the respective acetophenones in dry ether in the presence of anhydrous $AlCl_3$ as catalyst [8].

Preparation of p-chlorophenacyl phenylacetate

Method I. A mixture of tri-n-butylstannyl phenylacetate (0.85 g, 2 mmol) and *p*-chlorophenacyl bromide (0.234 g, 1 mmol) in 25 ml of acetone was refluxed for 6 h. The solvent was removed in a rotary evaporator, the residue was dissolved in dry ether, and 20 ml of 10% ammonium fluoride solution was added. The mixture was stirred for 20 min to precipitate all the tin compounds as the insoluble tri-n-butyltin fluoride, which was filtered off. The ether layer was separated, washed, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the products were separated on a column of silica gel with benzene as eluent.

Yield 0.05 g (17%): m.p. 85–86°C.

Method II. A mixture of tri-n-butylstannyl phenylacetate (0.47 g, 1.1 mmol), and *p*-chlorophenacyl bromide (0.234 g, 1 mmol) and benzyltriethylammonium chloride (0.12 g, 0.50 mmol) in 20 ml of acetonitrile was refluxed for 1 h. Work-up as in Method I gave the product.

Yield 0.213 g (74%); m.p. 85–86°C. IR (KBr), ν(CO) (cm^{-1}): 1740, 1690. UV (CH_3CN), λ_{max} (nm) (ε): 211.6 (13602) and 252 (15690). ^1H NMR ($CDCl_3$/TMS): 8.3–8.7 (m, 9H), 5.2 (s, 2H) and 3.76 (s, 2H) ppm. MS *m/e* (%) 288 (3), 196.9 (3), 170 (5), 150 (8), 141 (18), 139 (50), 119 (10), 118 (100), 91 (5), 58 (3).

Acknowledgements

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