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FULL PAPER

A sequential one-pot synthesis of functionalized esters and thioesters via ring opening-acylation of cyclic ethers and thioethers

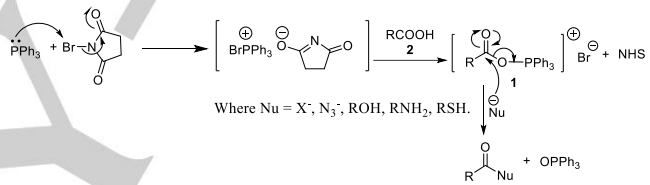
Purushothaman Gopinath[a,b,*] and Srinivasan Chandrasekaran[a,*]

Abstract: A one-pot protocol for the synthesis of functionalized esters and thioesters are reported from cyclic ethers/thioethers and carboxylic acids via acyloxyphosphonium salts as key intermediates. The reaction of styrene oxide with acyloxyphosphonium salts gave complete regioselectivity and good yields of the resulting functionalized ester, whereas cyclohexene oxide gave moderate yields. Styrene episulfide on the other hand gave good yields with moderate regioselectivty whereas cyclohexene sulfide gave quantitative yield of the corresponding thioesters. We have also shown an alternate procedure for the ring opening of THF to form 4-bromo butyl esters. All these reactions were carried out in the absence of catalyst, showing the synthetic versatility of our method.

Introduction

Main Ring opening of cyclic ethers and thioethers has great synthetic potential in organic synthesis as it gives direct access to bifunctionalised molecules.[1] Of particular importance are haloesters[2] which are used as key intermediates in the synthesis of many biologically useful molecules. [3] In contrast to halohydrins, haloesters are generally difficult to synthesize in a single step. One viable route for their synthesis is the ring opening of cyclic ethers with acid halides. Although, acylative cleavage of cyclic ethers with acid halides is known, in general they require catalysts such as Lewis acids,[4] lanthanide salts,[5] palladium/platinum complexes,[6,7] SmI_2[8] etc. or high pressures[9] with the exception of acyl iodides.[10] Some of the issues associated with the existing methods are as follows: (a) Lewis acids were used in stoichiometric amount and are either air sensitive (BCl_3),[4d] or longer reaction times ($ZnCl_2$, $FeCl_3$)[4a,b] with lower regioselectivity. (b) Lanthanide salts are hygroscopic and hence difficult to handle, whereas palladium, platinum & SmI_2 catalysts are expensive.

All these reactions also suffer from the additional limitation of using an acid halide, which in general are difficult to synthesize & handle (especially acyl iodides). It also involves an additional step for their synthesis from the corresponding carboxylic acids. Acyloxyphosphonium salts, **1** synthesized *in situ* from carboxylic acids (**2**) using PPh_3 and NBS (or NCS) are versatile intermediates in organic synthesis as they give direct access to acyl halides,[11] acyl azides,[12] esters,[13] thioesters,[14] and amides[15] (**Scheme 1**). Our group has already demonstrated the use of this salt for the generation of thiocarboxylate ions using benzyltriethylammonium tetrathiomolybdate[14a,b,c,16] for the formation of thioesters,[14a,b] Michael addition, epoxide and aziridine ring opening[14c] etc. Since these salts have an unutilized bromide ions, we worked out a synthetic strategy to use them for the ring opening of epoxides or thiiranes followed by acylation of the resulting alkoxide/thiolate in the same pot.



Scheme 1. Previous reports on the applications of acyloxyphosphonium salts.

Results and Discussion

We first investigated the opening of an epoxide (cyclic ether) with acyloxyphosphonium intermediates, 1. Accordingly, benzoic acid, triphenyl phosphine, NBS & styrene oxide were stirred together in dichloromethane for 7h. Interestingly, the expected bromo substituted ester, 4a was obtained regioselectively in 65% yield with ring opening at the benzylic carbon. Next, we screened different solvents for optimizing the reaction conditions and observed a maximum yield of 65% with dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$). With acetone and acetonitrile as solvents the yield was poor and with DMF & hexane the reaction didn't proceed even after stirring for 24 h. On the other hand with benzene as solvent, a moderate yield of the corresponding functionalized bromoester was obtained. Hence dichloromethane was chosen as the solvent for further studies (**Table 1**).

Encouraged by the optimized results, we extended the protocol to other carboxylic acids and in all the cases the ring opening occurred regioselectively at the benzylic position, showing the synthetic utility of the method (**Table 2**). We envisage the following mechanism, wherein styrene oxide, **3** first reacts with acyloxyphosphonium salt, **1** to form oxonium intermediate, **A**, which is followed by ring opening with bromide ion to form the corresponding bromoesters, **4** (**Scheme 2**). The correct regioisomer was identified using ^{1}H NMR and was further confirmed by single crystal X-ray analysis of compound **4e** (**fig 1**).

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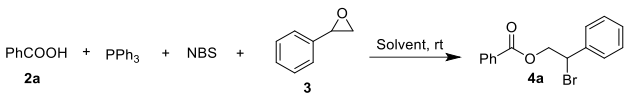
http://www.iisertirupati.ac.in/people/faculty/gopi.php
Supporting information for this article is given via a link at the end of the document.

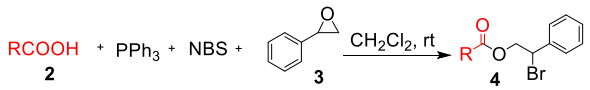
Table 1. Screening of solvents for the ring opening of styrene oxide [a]

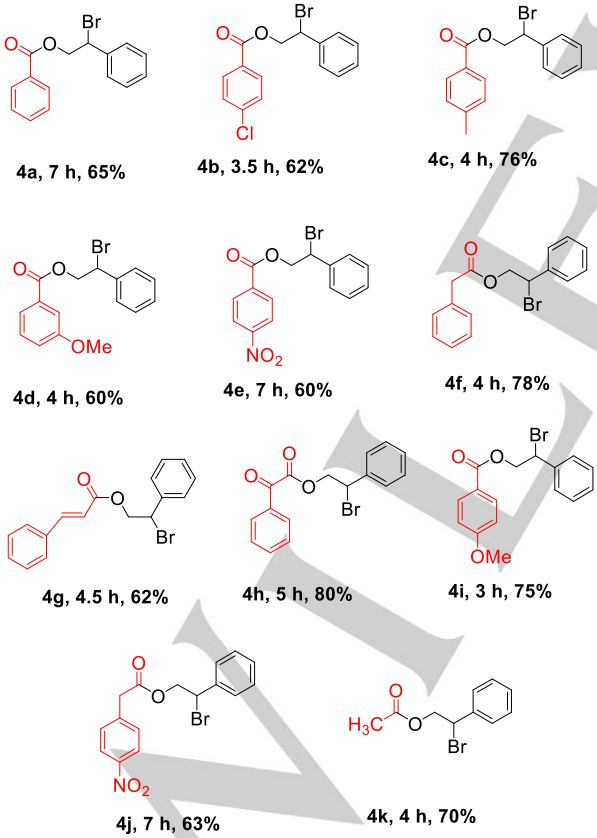


Solvent	Time (h)	Yield (%)
CH_2Cl_2	7	65
$CHCl_3$	7	65
CH_3CN	24	10
Acetone	24	15
DMF	24	No Reaction
Hexane	24	No
Benzene	7	55

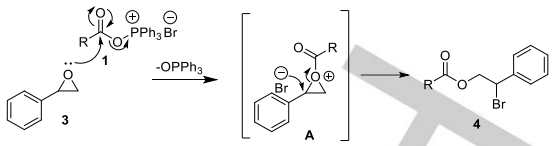
[a] Reaction was carried out with benzoic acid (1 mmol), PPh_3 (1.1 mmol), NBS (1.1 mmol) & styrene oxide (1.1 mmol) in the corresponding solvent (3 mL).

Table 2. Reaction of styrene oxide with various carboxylic acids.[a]





[a] Reaction was carried out with various carboxylic acids (1 mmol), PPh_3 (1.1 mmol), NBS (1.1 mmol) & Styrene oxide (1.1 mmol) in dichloromethane (3 mL) as solvent.



Scheme 2. Proposed mechanism for the formation of bromoesters

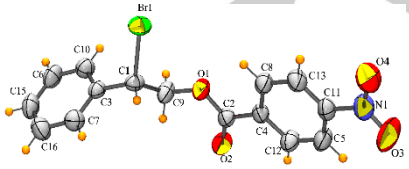
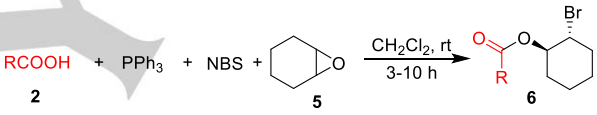
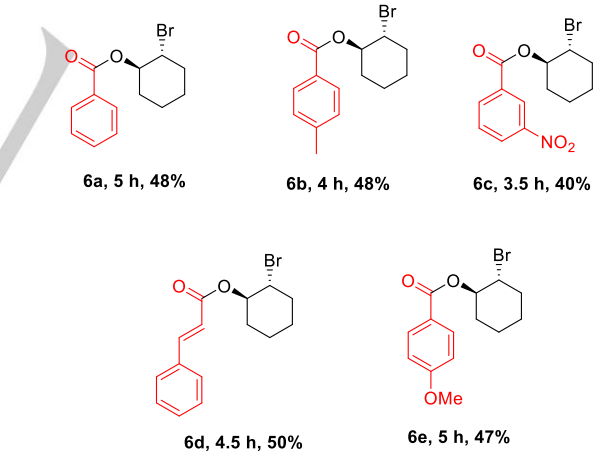


Fig 1. ORTEP diagram of compound **4e**

To demonstrate the generality of this methodology, the protocol was extended to other epoxides as well. With cyclohexene oxide, we obtained the corresponding *trans*-bromo subsituted ester, **6**. The yields were only moderate due to the formation of side product from dehydrohalogenation (**Table 3**).

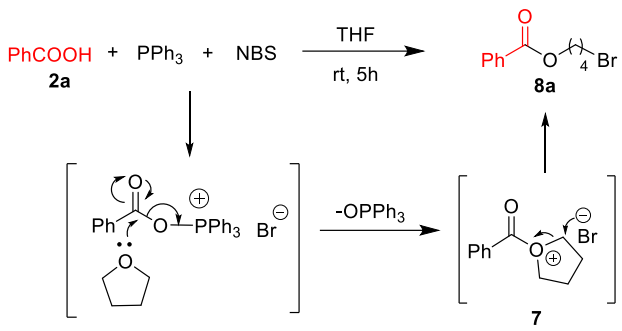
Table 3. Reaction of cyclohexene oxide with various carboxylic acids.[a]





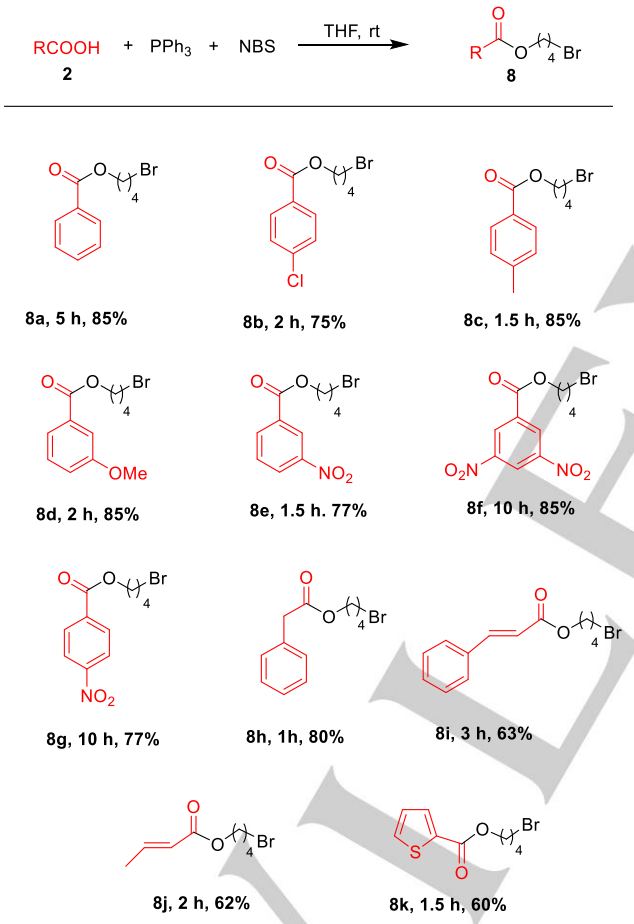
[a] Reaction was carried out with various carboxylic acids (1 mmol), PPh_3 (1.1 mmol), NBS (1.1 mmol) & cyclohexene oxide (1.1 mmol) in dichloromethane (3 mL) as solvent

We then attempted the ring opening of tetrahydrofuran (THF, a cyclic ether) under similar conditions to show the synthetic versatility of our protocol. Again, the reaction is believed to proceed via an oxonium intermediate, **7** (which activates the THF ring for facile opening by bromide ion). With benzoic acid as substrate we obtained the corresponding bromo substituted ester, 8a in 85% yield. (**Scheme 3**).



Scheme 3. Proposed mechanism for THF ring opening.

Table 4. Reaction of THF with various carboxylic acids.[a]



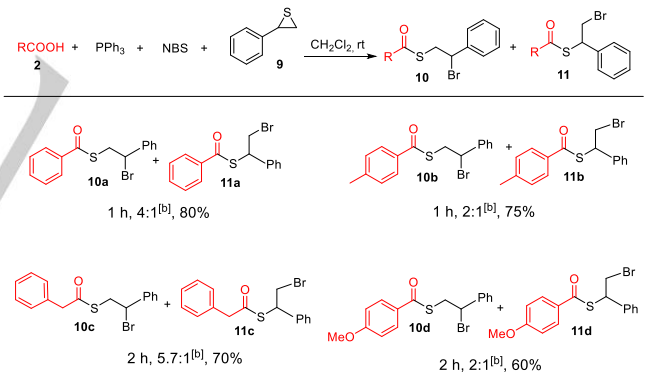
[a] Reaction was carried out with various carboxylic acids (1 mmol), PPh_3 (1.1 mmol), & NBS (1.1 mmol), in THF (3 mL) as solvent.

Although similar types of reactions were reported with THF using zinc bromide[4f] and allyl samarium bromide[4e] as catalyst in dichloromethane as solvent, herein we report an alternate method for their synthesis without any catalyst. In the present protocol, THF was used as solvent and NBS was used as the bromide source instead of Br_2 without any additional catalysts. The reaction with benzoic acid as substrate gave 85% yield of the corresponding bromo substituted ester, which is superior to the reactions reported with catalysts (60-65%). We extended the protocol to other carboxylic acids to demonstrate the generality of the method and the results are summarized in **Table 4**. In all the cases, the final bromo substituted esters (**8a-k**) were obtained in good to excellent yields (60-85%).

Finally, we attempted the ring opening of thiiranes using the same protocol. Although ring opening of epoxides to bromo substituted esters are documented, the corresponding reaction with thiiranes to form bromo substituted thioesters was less studied.[17] Since thioesters are important synthetic intermediates in organic synthesis particularly in peptide coupling,[18] acyl transfer,[19] as protecting group for thiols,[20] and as key intermediates in various biological process,[21] we adapted the same protocol for the synthesis of bromo substituted thioesters from thiiranes.

Accordingly styrene episulphide **9**,[22] PPh_3, and NBS were treated with various carboxylic acids, to afford the corresponding bromo substituted thioesters in good yields but with a lower regioselectivity. We speculate that since the benzylic position of styrene episulfide is less reactive than styrene oxide, moderate regioselectivity was observed. The results of this study are summarized in **Table 5**.

Table 5. Reaction of styrene episulfide with various carboxylic acids.[a]

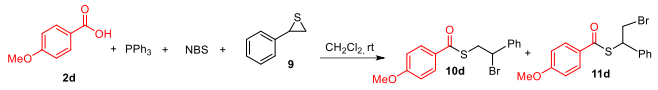


[a] Reaction was carried out with various carboxylic acids (1 mmol), PPh_3 (1.1 mmol), NBS (1.1 mmol), & styrene episulfide (1.1 mmol) in dichloromethane (3 mL) as solvent. b Based on ^1H NMR.

In order to further improve the selectivity we studied the effect of Lewis acid on the regioisomeric ratio using *p*-methoxy benzoic acid, as the starting material. With 20 mol % of lithium perchlorate there was no change in the ratio of regioisomers but with 1 equiv of lithium perchlorate the ratio increased to 4:1 from 2:1 albeit with lower yield (50%). With 2 equiv of lithium perchlorate both the ratio and yield decreased to 3:1 and 40% respectively and with $BF_3.OEt_2$ (1equiv) as Lewis acid the ratio increased to 7:1 while the yield dropping down to 25% (**Table 6**). We presume that Lewis acids increase the reactivity of benzylic carbon by coordination to the sulfur atom of styrene episulfide (and polarize the C-S bond),

resulting in increased reigioselectivity but the yields dropped due to the formation of complex side products.

Table 6. Effect of Lewis acids on the regioisomeric ratio of ring opening of styrene episulfide.[a]

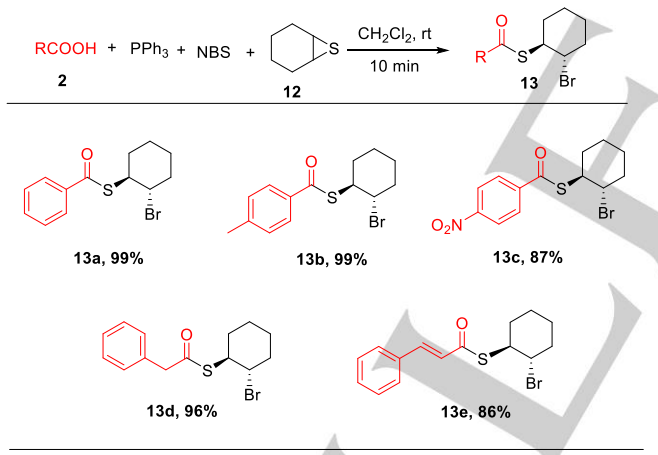


Catalysts	Regioisomeric ratio **10d : 11d**	Yield (%)
No catalyst	**2 : 1**	60
$LiClO_4$ (0.2equiv)	**2 : 1**	55
$LiClO_4$ (1.0equiv)	**4 : 1**	50
$LiClO_4$ (2.0equiv)	**3 : 1**	40
$BF_3.OEt_2$ (1.0equiv)	**7 : 1**	25

[a] Reaction was carried out with various carboxylic acids (1 mmol), PPh_3 (1.1 mmol), NBS (1.1 mmol), styrene episulfide (1.1 mmol) & corresponding Lewis acids in dichloromethane (3mL) as solvent.

Later we extended the same protocol for ring opening of cyclohexene sulfide and the corresponding *trans*-bromo substituted thioesters were obtained in almost quantitative yields. The reactions were generally fast and completed within 10 mins (**Table 7**).

Table 7. Reaction of cyclohexene sulfide with various carboxylic acids.[a]



[a] Reaction was carried out with various carboxylic acids (1 mmol), PPh_3 (1.1 mmol), NBS (1.1 mmol), cyclohexene oxide (1.1 mmol) in dichloromethane (3mL) as solvent

Conclusions

In conclusion, a variety of bromo substituted esters and thioesters have been synthesized using acyloxyphosphonium salt as a common intermediate, thereby showing the synthetic utility of this protocol. The reactions were generally regioselective, especially styrene oxide, which showed complete regioselectivity with the ring opening occurring at the benzylic position. Both cyclohexene oxide and cyclohexene sulfide gave the corresponding bromo esters and thioesters exclusively with *trans* geometry. Ring opening of thiiranes was very facile and gave quantitative yield of the corresponding bromo substituted thioesters.

Experimental Section

General Procedures. All reactions were carried out in oven-dried apparatus using dry solvents under anhydrous conditions, unless otherwise noted. Reaction mixtures were stirred magnetically unless otherwise stated. Commercial grade solvents were distilled and dried according to literature procedures ("Purification of laboratory chemicals", 3rd Ed., D. D. Perrin, W. L. F. Armarego, Pergamon Press, Oxford, 1988). Analytical TLC was performed on commercial plates coated with silica gel GF254 (0.25 mm). Silica gel (230 - 400 mesh) was used for column chromatography. Melting points determined are uncorrected. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. NMR spectra were recorded on 300 or 400 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations explain the multiplicity s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a FT-IR spectrometer. High-resolution mass spectra (HR-MS) were recorded on a Micromass Q-TOF mass spectrometer.

General procedure for the formation of 1,2 bromoesters: N-bromosuccinimide (0.195g, 1.1 mmol) was added to a well stirred solution of the corresponding acid (1 mmol) and PPh_3 (0.288g, 1.1 mmol) in CH_2Cl_2 (3mL). After 2 minutes the corresponding epoxide (1.1 mmol) was added to it. Completion of the reaction was monitored through TLC. The crude mixture was then purified by column chromatography. Compounds 4a, 6a 4g,[23] 4k,[24] 6a,[25] 6d,[23] & 6e[26] are reported are reported.

2-bromo-2-phenylethyl 4-chlorobenzoate (**4b)**: Yield: 62% (210.5 mg); IR (Neat) 1724, 1267, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 8.7 Hz, 2H), 7.48 – 7.33 (m, 7H), 5.25 (t, J = 7.2 Hz, 1H), 4.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 139.8, 137.9, 131.0, 129.1, 128.9, 128.8, 127.9, 127.8, 68.0, 49.8; HR - MS m/z: calcd for $C_{15}H_{12}BrClO_2Na^+$ [M+Na^+]: 360.9607; found: 360.9600.

2-bromo-2-phenylethyl 4-methylbenzoate (**4c)**: Yield: 76% (242.6 mg); IR (Neat): 1720, 1269, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 8.1 Hz, 2H), 7.48 – 7.45 (m, 2H), 7.39 – 7.25 (m, 3H), 7.21 (d, J = 7.5 Hz, 2H), 5.26 (t, J = 7.5 Hz, 1H), 4.77 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 144.0, 138.1, 129.7, 129.1, 128.9, 128.8, 127.8, 126.8, 67.7, 50.1, 12.6; HR - MS m/z: calcd for $C_{16}H_{15}BrO_2Na^+$ [M+Na^+]: 341.0153; found: 341.0143.

2-bromo-2-phenylethyl 3-methoxybenzoate (**4d)**: Yield: 60% (201.1 mg); IR (Neat): 1724, 2919, 1274 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 – 7.07 (m, 9H), 5.25 (t, J = 7.5 Hz, 1H), 4.78 (m, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 159.5, 138.1, 130.8, 129.4, 129.0, 128.8, 127.8, 122.1, 119.8, 114.1, 67.9, 55.3, 49.9; HR - MS m/z: calcd for $C_{16}H_{15}BrO_3Na^+$ [M+Na^+]: 357.0102; found: 357.0084.

2-bromo-2-phenylethyl 4-nitrobenzoate (**4e)**: yellow solid; Yield: 60% (210.1 mg); m. p: 95 ˚C; IR (Neat): 1730, 1528, 1268 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H), 7.49 – 7.34 (m, 5H), 5.28 (t, J = 7.5 Hz, 1H), 4.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9, 150.6, 137.6, 134.8, 130.8, 129.2, 128.9, 127.7, 123.5,

68.5, 49.5; Anal. Calcd for $C_{15}H_{12}BrNO_4$: C, 51.45; H, 3.45; N,4.00; Found: C, 51.32; H, 3.42; N, 4.09.

2-bromo-2-phenylethyl 2-phenylacetate (**4f**): Yield: 78% (249.0 mg); IR (Neat): 1740, 1142cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 10H), 5.09 (t, J = 7.2 Hz, 1H), 4.58 (m, 2H), 3.59 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 137.9, 133.4, 129.2, 128.8, 128.7,128.5, 127.7, 127.1, 67.6, 49.6, 41.0; HR - MS m/z: calcd for $C_{16}H_{15}BrO_2Na^+$ [M+Na$^+$]: 341.0153; found: 341.0182.

2-bromo-2-phenylethyl 2-oxo-2-phenylacetate **(4h)**: Yield: 80% (266.5 mg); IR (Neat): 1744, 1689, 1194, 1173 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.81 – 7.77 (m, 2H), 7.65 – 7.60 (m, 1H), 7.49 – 7.36 (m, 7H), 5.24 (t, J = 7.5 Hz, 1H), 4.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.6, 162.9, 137.3, 135.0, 132.0, 130.0, 129.3, 129.0, 128.9, 127.9, 68.2, 48.7; HR - MS m/z: calcd for $C_{16}H_{13}BrO_3Na^+$ [M+Na$^+$]: 354.9946; found: 354.9926.

2-bromo-2-phenylethyl 4-methoxybenzoate (**4i)**: Yield: 75% (251.4 mg); IR (Neat): 1715, 1605, 1258 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 6.9 Hz, 2H), 7.48 – 7.32 (m, 5H), 6.89 (d, J = 6.9 Hz, 2H), 5.26 (t, J = 7.2 Hz, 1H), 4.76 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 163.6, 138.1, 131.7, 128.9, 128.8, 127.8, 121.8, 113.6, 67.6, 55.4, 50.2; HR - MS m/z: calcd for $C_{16}H_{15}BrO_3Na^+$ [M+Na$^+$]: 357.0102; found: 357.0105.

2-bromo-2-phenylethyl 2-(4-nitrophenyl)acetate (**4j)**: Yield: 63% (229.4 mg); IR (Neat) 1740, 1519, 1347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, J = 8.7 Hz, 2H), 7.32 – 7.30 (m, 7H), 5.08 (t, J = 7.5 Hz, 1H), 4.60 (m, 2H), 3.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 147.1, 140.6, 137.6, 130.2, 129.0, 128.8, 127.7, 123.6, 67.7, 49.2, 40.7; Anal. Calcd for $C_{16}H_{14}BrNO_4$: C, 52.77; H, 3.87; N,3.850; Found: C, 52.97; H, 4.23; N, 3.90.

trans-2-bromocyclohexyl 4-methylbenzoate **(6b)**: Yield: 48% (142.6 mg); IR (Neat) 1722, 1271, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 5.11 (dt, J_1 = 4.2 Hz, J_2 = 9.0 Hz, 1H), 4.15 (dt, J_1 = 4.2 Hz, J_2 = 10.2 Hz, 1H), 2.42 (s, 3H), 2.40 (m, 1H), 2.27 (m, 1H), 1.89 (m, 3H), 1.49 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 143.7, 129.7, 129.1, 127.5, 76.1, 52.7, 35.5, 31.1, 25.4, 23.3, 21.7; HR - MS m/z: calcd for $C_{14}H_{17}BrO_2Na^+$ [M+Na$^+$]: 319.0307; found: 319.0307.

trans-2-bromocyclohexyl 3-nitrobenzoate (**6c)**: Yield: 40% (131.3 mg); IR (Neat) 1719, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (t, J = 1.5 Hz, 1H), 8.46 – 8.39 (m, 2H), 7.68 (t, J = 7.8 Hz, 1H), 5.17 (m, 1H), 4.16 (m, 1H), 2.37 (m, 2H), 1.91 (m, 4H), 1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 148.5, 135.5, 131.9, 129.6, 127.5, 124.7, 77.7, 52.5, 35.8, 31.5, 25.7, 23.5; HR - MS m/z: calcd for $C_{13}H_{14}BrNO_4Na^+$ [M+Na$^+$]: 350.0002; found: 350.0003.

General procedure for the formation of 1,4 bromoesters: To a well stirred solution of carboxylic acid (1 mmol) and PPh_3 (0.288g, 1.1 mmol) in THF (3mL) was added N-bromosuccinimide (0.195g, 1.1mmol). Completion of the reaction was monitored through TLC. The crude mixture was then purified by column chromatography. Compounds 8a, 6a 8b,4f 8c,4f 8g,4f 8h,[27] 8i,4f 8j,[28] & 8k[29] are reported.

4-bromobutyl 3-methoxybenzoate **(8d)**: Yield: 85% (244.1 mg); IR (Neat): 1718, 1600, 1587, 1280 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.65 – 7.55 (m, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.12 – 7.09 (m, 1H), 4.35 (t, J = 6.0 Hz, 2H), 3.85 (s, 3H), 3.48 (t, J = 6.5 Hz, 2H), 1.99 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 166.3, 159.5, 131.4, 129.3, 121.8, 119.3, 114.0, 64.0, 55.4, 33.1, 29.3, 27.3; HR - MS m/z: calcd for $C_{12}H_{15}BrO_3Na^+$ [M+Na$^+$]: 309.0102; found: 309.0102.

4-bromobutyl 3-nitrobenzoate (**8e)**: Yield: 77% (232.7 mg); IR (Neat): 1725, 1533, 1350 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.55 (t, J = 1.8 Hz, 1H), 8.45 – 8.36 (m, 2H), 7.68 (t, 8.1 Hz, 1H), 4.43 (t, J = 6.0 Hz, 2H), 3.50 (t, J = 6.3 Hz, 2H), 2.11 – 1.95 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 164.4, 148.2, 135.2, 131.9, 129.6, 127.4, 124.5, 64.9, 32.9, 29.2, 27.3; HR - MS m/z: calcd for $C_{11}HR_{12}BrNO_4Na^+$ [M+Na$^+$]: 323.9847; found: 323.9846.

4-bromobutyl 3,5-dinitrobenzoate (**8f)**: Yield: 85% (295.0 mg); IR (Neat): 1731, 1544, 1346, 1282 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 9.24 (t, J = 2.1 Hz, 1H), 9.16 (d, J = 2.1 Hz, 2H), 4.15 (t, J= 6 Hz, 2H), 3.1 (t, J = 5.9 Hz, 2H), 2.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 162.4, 148.6, 133.8, 129.4, 122.4, 66.0, 32.7, 29.0, 27.2; Anal. Calcd for $C_{11}H_{11}BrN_2O_6$: C, 38.06; H, 3.19; N,8.07; Found: C, 37.81; H, 3.29; N, 8.24.

General procedure for the formation of 1,2 bromothioesters: N-bromosuccinimide (0.195g, 1.1 mmol) was added to a well stirred solution of the corresponding acid (1 mmol) and PPh_3 (0.288g, 1.1 mmol) in CH_2Cl_2 (3mL). After 2 minutes the corresponding thiirane (1.1 mmol) was added to it. Completion of the reaction was monitored through TLC. The crude mixture was then purified by column chromatography. Regioisomers **10** & **11** were inseparable.

2-bromo-2-phenylethyl benzothioate (**10a)** & 2-bromo-1-phenylethyl benzothioate **(11a)**: (80 : 20). Yield: 80% (257.0 mg); IR (Neat) 1666, 1582, 1208, 903 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.94 - 7.89 (m, 2H), 7.57 – 7.52 (m, 1H), 7.45 – 7.30 (m, 10H), 5.12 (dd, J_1 = 7.2 Hz, J_2 = 9.0 Hz, 1H), 5.06 (dd, J_1 = 4.8 Hz, J_2 = 9.9 Hz, 0.23H), 4.03 – 3.93 (m, 1.3H), 3.85 – 3.77 (m, 1.3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): 190.4, 140.1, 136.5, 133.7, 128.7, 128.6, 128.3, 128.1, 127.8, 127.6, 127.3, 51.8, 48.8, 37.5, 34.7; Anal. Calcd for $C_{15}H_{13}BrOS$: C, 56.08; H, 4.08; S, 9.98 Found: C, 55.78; H, 4.11; S, 10.40.

2-bromo-2-phenylethyl 4-methylbenzothioate (**10b)** & 2-bromo-1-phenylethyl 4-methylbenzothioate **(11b)**: (67 : 33). Yield: 75% (251.4 mg); IR (Neat) 1661, 1605, 1207, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.82 - 7.79 (m, 1H), 7.70 – 7.64 (m, 1H), 7.55 – 7.31 (m, 5H), 7.25 – 7.20 (m, 2H), 5.12 (dd, J_1 = 6.9 Hz, J_2 = 8.1 Hz, 0.6H), 5.05 (dd, J_1 = 5.1 Hz, J_2 = 10.2 Hz, 0.35H), 4.02 – 3.94 (m, 1H), 3.85 – 3.76 (m, 1H) 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): 190.0, 144.6, 144.2, 132.1, 129.3, 128.8, 128.2, 128.1, 127.6, 127.4, 51.8, 48.6, 37.5, 34.8, 21.6; Anal. Calcd for $C_{16}H_{15}BrOS$: C, 57.32; H, 4.51; S, 9.56 Found: C, 57.61; H, 4.62; S, 9.73.

2-bromo-2-phenylethyl 2-phenylethanethioate **(10c)** & 2-bromo-1-phenylethyl 2-phenylethanethioate **(11c)**: (85 : 15). Yield: 70% (234.7 mg); IR (Neat) 1668, 1494, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ 7.40 - 7.19 (m, 12H), 4.97 (dd, J_1 = 6.8 Hz, J_2 = 8.8 Hz, 1H), 4.81 (dd, J_1 = 4.8 Hz, J_2 = 10.0 Hz, 0.18H), 3.83 – 3.73 (m, 3.2H), 3.68 (dd, J_1 = 4.0 Hz, J_2 = 6.0 Hz, 0.4H), 3.62 (dd, J_1 = 8.8 Hz, J_2 = 13.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): 195.9, 139.8, 133.1, 129.6, 129.4, 129.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.5, 126.6, 51.5, 50.3, 50.2, 48.9, 47.7, 34.6; Anal. Calcd for $C_{16}H_{15}BrOS$: C, 57.32; H, 4.51; S, 9.56 Found: C, 57.70; H, 4.72; S, 9.68.

2-bromo-2-phenylethyl 4-methoxybenzothioate (**10d)** & 2-bromo-1-phenylethyl 4-methoxybenzothioate **(11d)**: (67 : 33). Yield: 60% (210.7 mg); IR (Neat) 1658, 1603, 1509, 1257 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.93 - 7.88 (m, 2H), 7.45 – 7.26 (m, 5H), 6.93 – 6.89 (m, 2H), 5.12 (dd, J_1 = 6.9 Hz, J_2 = 8.7 Hz, 0.67H), 5.04 (dd, J_1 = 5.1 Hz, J_2 = 10.2 Hz, 0.33H), 4.02 – 3.94 (m, 1.H), 3.86 (d, 3H) 3.83 – 3.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): 188.8, 188.3, 164.0, 163.9, 140.1, 138.0, 132.2, 132.1, 129.5, 129.2, 128.7, 128.2, 128.0, 127.5, 113.8, 113.7, 55.4, 52.0,

48.5, 37.3, 34.9; Anal. Calcd for $C_{16}H_{15}BrO_2S$: C, 54.71; H, 4.30; S, 9.11 Found: C, 54.98; H, 4.46; S, 9.25.

trans-2-bromocyclohexyl benzothioate (**13a)**: Yield: 99% (296.2 mg); IR (Neat): 1663, 1445, 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.98 – 7.60 (m, 2H), 7.60 – 7.55 (m, 1H), 7.48 – 7.42 (m, 2H), 4.34 (dt, J_1 = 3.6 Hz, J_2 = 6.9 Hz, 1H), 4.14 – 4.08 (m, 1H), 2.47 – 2.27 (m, 2H), 2.04 – 1.94 (m, 1H), 1.89 – 1.43 (m,5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 190.2, 136.9, 133.4, 128.6, 127.3, 54.5, 48.5, 34.4, 30.2, 24.1, 23.5; HR - MS m/z: calcd for $C_{13}H_{15}BrOSNa^+$ [M+Na^+]: 320.9923; found: 320.9908.

trans-2-bromocyclohexyl 4-methylbenzothioate (**13b)**: Yield: 99% (310 mg); IR (Neat): 1661, 1607, 1446, 1206, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 25°C): δ 7.86 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.37 – 4.33 (m, 1H), 4.13 – 4.08 (m, 1H), 2.44 – 2.39 (m, 4H), 2.34 – 2.28 (m, 1H), 2.01 – 1.96 (m, 1H), 1.84 – 1.81 (m, 1H), 1.71 – 1.62 (m, 3H), 1.50 – 1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ 189.9, 144.4, 134.3, 129.3, 127.4, 54.6, 48.1, 34.3, 30.0, 24.0, 23.3, 21.7; HR - MS m/z: calcd for $C_{14}H_{17}BrOSNa^+$ [M+Na^+]: 335.0081; found: 335.0093.

trans-2-bromocyclohexyl 4-nitrobenzothioate (**13c)**: Yield: 87% (299.5 mg); IR (Neat): 1660, 1605, 1525, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.31 (d, J = 8.7 Hz, 2H), 8.12 (d, J = 8.7 Hz, 2H), 4.30 (dt, J_1 = 3.6 Hz, J_2 = 7.5 Hz, 1H), 4.16 – 4.10 (m, 1H), 2.47 – 2.30 (m, 2H), 2.07 – 1.96 (m, 1H), 1.89 – 1.46 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 188.8, 150.6, 141.4, 128.3, 123.8, 53.7, 49.5, 35.0, 30.6, 24.2, 23.6; Anal. Calcd for $C_{13}H_{14}BrNO_3S$: C, 45.36; H, 4.10; S, 9.32; N, 4.07 Found: C, 45.74; H, 4.30; S, 9.74; N, 4.23.

trans-2-bromocyclohexyl 2-phenylethanethioate (**13d)**: Yield: 96% (300.7 mg); IR (Neat): 1692, 1495, 1445, 1188, 999, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.36 – 7.25 (m, 5H), 4.20 – 4.17 (m, 1H), 3.89 – 3.82 (m, 3H), 2.31 – 2.17 (m, 2H), 1.96 – 1.71 (m, 2H), 1.59 – 1.38 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 195.5, 133.3, 129.5, 128.6, 127.4, 54.3, 50.5, 48.6, 34.4, 30.0, 24.0, 23.4, 21.7; HR - MS m/z: calcd for $C_{14}H_{17}BrOSNa^+$ [M+Na^+]: 335.0081; found: 335.0071.

trans-2-bromocyclohexyl) (E)-3-phenylprop-2-enethioate (**13e)**: Yield: 86% (279.7 mg); IR (Neat): 1672, 1654, 1615, 1447, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25°C): δ 7.62 (d, J = 15.9 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.40 – 7.38 (m, 3H), 6.68 (d, J = 15.9 Hz, 1H), 4.29 (dt, J_1 = 3.4 Hz, J_2 = 6.9 Hz, 1H), 4.06 – 4.00 (m, 1H), 2.43 – 2.24 (m, 2H), 2.02 – 1.92 (m, 1H), 1.87 – 1.74 (m, 1H), 1.70– 1.58 (m, 3H), 1.52 – 1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 188.0, 140.9, 134.0, 130.6, 128.9, 128.4, 124.6, 54.5, 48.3, 34.5, 30.2, 24.1, 23.5; Anal. Calcd for $C_{15}H_{17}BrOS$: C, 55.39; H, 5.27; S, 9.86 Found: C, 55.80; H, 4.90; S, 9.32.

CCDC-689879 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: acylation • multicomponent reactions • synthetic methods • functionalized esters • Thioesters

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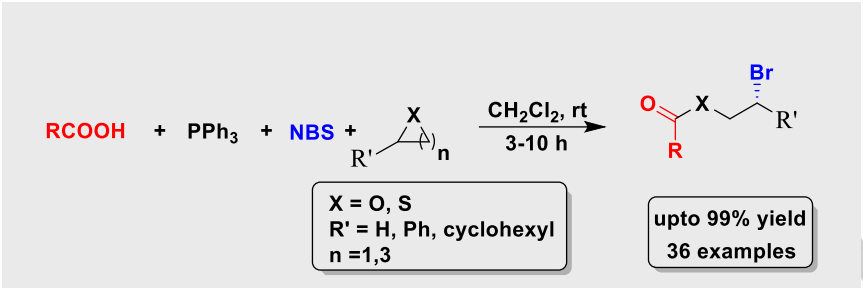

Functionalized esters and thioesters were synthesized from carboxylic acids and cyclic ethers/thioethers via acyloxyphosphonium salts as key intermediates. The resulting esters were obtained in high yields and with complete regioselectivity (for styrene oxide). On the other hand thioesters were obtained in good yields but with moderate regioselectivity (for styrene episulfide).

Multicomponent reaction*

Purushothaman Gopinath[a,b,*] *Srinivasan Chandrasekaran*[a]

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A sequential one-pot synthesis of functionalized esters and thioesters via ring opening-acylation of cyclic ethers and thioethers.