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Hydrolytic Reactions on Polyphenolic Perpropanoates by Porcine Pancreatic Lipase Immobilized in Microemulsion-based Gels

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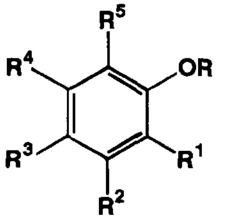
Abstract: Porcine pancreatic lipase (PPL) has been immobilized in microemulsion-based gels (MBGs). Highly selective and efficient deacylation of di/trihydric phenolic perpropanoates has been observed on incubating them with immobilized PPL. These reactions can find general utility in Synthetic Organic Chemistry. Copyright © 1996 Elsevier Science Ltd

Polyphenolics occur widely in nature and being the secondary metabolites of plants, many of their analogs possess a variety of biological activities. Suitably substituted polyhydric phenols are used as starting materials for the synthesis of different classes of natural polyphenolics *viz.* chalcones, flavones, flavanones, isoflavonoids, coumarins, xanthones, catechins, etc. Selective protection and deprotection steps are often required to achieve the total synthesis of these compounds, which are rather difficult, moreover they increase the number of steps and decrease the net yields thus making the overall synthesis quite cumbersome. In order to ease the problems of protection/deprotection in the synthesis of biopolyphenolics, we have studied earlier the regioselective deacetylation reactions in polyacetoxy aryl-methyl ketones by lipases in organic solvents.[1-3] From the preliminary studies it was postulated that nuclear carbonyl group present in the substrate forms dynamic Schiff's base type complex, which we believe is responsible for regioselective deacetylation.[2] Selectivity in enzyme-mediated protection/deprotection of phenolic groups in polyhydroxy/ polyacyloxy benzene derivatives, lacking a directly attached nuclear ketonic carbonyl group in dry organic solvents is not observed as reported by us earlier.[3] However due to the potential applications of such compounds, both in the Laboratory and in Industry, we envisaged to employ lipases in different media for attaining selectivity in the hydrolysis of peracylated polyhydric phenols.

Biotechnological applications of microemulsions have received a great deal of attention since the discovery that enzymes could be solubilized in cores of water/oil (w/o) microemulsion droplets with retention of activity and stability.[4,5] A large number of enzymes have been solubilized in w/o microemulsion systems and their catalytic behaviour has been studied, the microdomains favour selective partitioning of substrates or products which can, in turn affect the equilibrium position of the reaction.

From practical standpoint, pool-entrapped enzymes have potential utility in enzyme-mediated reactions involving water-insoluble compounds.[6] Though microemulsion systems are highly advantageous for enzyme-catalyzed reactions in non-aqueous media while maintaining aqueous environment around enzyme, however scale-up of such processes is problematic.[7] Alternative approaches have been developed involving the use of gelatin solubilized in microemulsion-based gels (MBGs), it has three dimensional network having transparent single phase which can be used to immobilize enzymes for synthetic applications.[8] To date only a few papers have been published on the synthetic applications of lipases in micro-emulsion based gels (MBGs).[9] In this article, we report highly selective/ regioselective hydrolysis of perpropanoates of eight different di/trihydric phenols catalysed by the commonly used inexpensive lipase, i.e. porcine pancreatic lipase (PPL)[10] in MBGs on a multigram scale. We have used polyphenolic perpropanoates instead of peracetates, it is a general observation in lipase mediated de-esterification reactions that the selectivity of the lipase increases with the increase in number of carbon atoms of the alkyl chain of the acyl moiety.[11]



1 $R=COCH_2CH_3$, $R^1=OCOCH_2CH_3$, $R^2=R^3=R^4=R^5=H$
2 $R=COCH_2CH_3$, $R^1=R^3=R^4=R^5=H$, $R^2=OCOCH_2CH_3$
3 $R=COCH_2CH_3$, $R^1=R^2=R^4=R^5=H$, $R^3=OCOCH_2CH_3$
4 $R=COCH_2CH_3$, $R^1=R^3=R^5=H$, $R^2=R^4=OCOCH_2CH_3$
5 $R=COCH_2CH_3$, $R^1=CH_3$, $R^2=OCOCH_2CH_3$, $R^3=R^4=R^5=H$
6 $R=COCH_2CH_3$, $R^1=CH_3$, $R^2=R^3=R^5=H$, $R^4=OCOCH_2CH_3$
7 $R=COCH_2CH_3$, $R^1=C(CH_3)_3$, $R^2=R^4=R^5=H$, $R^3=OCOCH_2CH_3$
8 $R=COCH_2CH_3$, $R^1=R^5=H$, $R^2=R^4=OCH_3$, $R^3=OCOCH_2CH_3$
9 $R=R^2=R^3=R^4=R^5=H$, $R^1=OCOCH_2CH_3$
10 $R=R^1=R^3=R^4=R^5=H$, $R^2=OCOCH_2CH_3$
11 $R=R^1=R^2=R^4=R^5=H$, $R^3=OCOCH_2CH_3$
12 $R=R^1=R^3=R^5=H$, $R^2=R^4=OCOCH_2CH_3$
13 $R=R^3=R^4=R^5=H$, $R^1=CH_3$, $R^2=OCOCH_2CH_3$
14 $R=R^2=R^3=R^5=H$, $R^1=CH_3$, $R^4=OCOCH_2CH_3$
15 $R=R^2=R^3=R^5=H$, $R^1=CH_3$, $R^4=OH$
16 $R=COCH_2CH_3$, $R^1=CH_3$, $R^2=R^3=R^5=H$, $R^4=OH$
17 $R=R^2=R^4=R^5=H$, $R^1=C(CH_3)_3$, $R^3=OCOCH_2CH_3$
18 $R=COCH_2CH_3$, $R^1=C(CH_3)_3$, $R^2=R^4=R^5=H$, $R^3=OH$
19 $R=R^1=R^5=H$, $R^2=R^4=OCH_3$, $R^3=OCOCH_2CH_3$
20 $R=COCH_2CH_3$, $R^1=R^5=H$, $R^2=R^4=OCH_3$, $R^3=OH$

The perpropanoates (**1**-**8**), dissolved in benzene were allowed to react with the lipase in MBGs[12] and the reactions were monitored on TLC plates (coated with silica gel). Maximum (partial) deprotection of propanoyloxy groups was observed after the indicated reaction time (Table 1); after prolonged contact of the substrates with the lipase immobilised in MBGs, the yields of the selectively deprotected products did not increase, instead the parent di/trihydric phenols started forming. The reactions were quenched by filtering off the lipase immobilised in MBGs, the solvent was removed *in vacuo* from the filterate and the products were purified by repeated column chromatography and/or prep TLC to yield the compounds **9-14**, **17** and **19**, which were characterised from their ^{1}H NMR, IR and mass spectral data.[13] As per our scrutiny of literature, all the compounds except **1**[14] and **3**[15] are new and being reported by us for the first time, however no spectral data is reported even for the compounds **1** and **3**.

Table 1. Hydrolytic reactions catalysed by PPL immobilized in MBGs in dry benzene at 28-30°C on the peracylated polyphenolics 1-8.

Substrate	**Reaction time (hrs)**	**Product, % conversion as determined by relative quantification of reactants and products by analytical TLC (% yield[16])**
Catechol dipropanoate(**1**)	2	Catechol monopropanoate(**9**),75(20)
Resorcinol dipropanoate(**2**)	2	Resorcinol monopropanoate(**10**),70(25)
Hydroquinone dipropanoate(**3**)	2	Hydroquinone monopropanoate(**11**),78(15)
Phloroglucinol tripropanoate(**4**)	2	Phloroglucinol dipropanoate(**12**),60(35)
2,6-Dipropanoyloxytoluene(**5**)	4	2-Hydroxy-6-propanoyloxytoluene(**13**),50(40)
2,4-Dipropanoyloxytoluene(**6**)	4	2-Hydroxy-4-propanoyloxytoluene(**14**),55(40)
2-*t*-Butylhydroquinone dipropanoate(**7**)	5	2-*t*-Butyl-4-propanoyloxyphenol (**17**),55(35)
2,6-Dimethoxyhydroquinone dipropanoate(**8**)	5	3,5-Dimethoxy-4-propanoyloxyphenol(**19**),65(25)

The monodeacylated products of compounds **1-5**, namely the compounds **9-13**, respectively are symmetrical and were easily characterised from their IR,^{1}H NMR and mass spectral data.[13] The product of deacylation reaction over compound **6** was identified as 2-hydroxy-4-propanoyloxytoluene(**14**) on the basis that in its ^{1}H NMR spectrum, the C-3 proton which is *meta* coupled moved upfield and appeared at δ 6.3, while in the starting dipropanoate **6**, the same proton appeared at δ 7.0. However, no significant change in the chemical shift values was observed for the C-5 and C-6 protons, thus indicating that deacylation has occurred at the C-2 position. The appearance of H-3 at δ 6.2 in 2,4-dihydroxytoluene (**15**) further substantiated that deacylation in compound **6** has occurred at the C-2 position. The alternative structure 2-propanoyloxy-4-hydroxytoluene (**16**) for the product was ruled out as in this compound, both the H-3 and H-5 should have moved upfield as compared to those in the starting compound **6**. The product of enzymatic deacylation on compound **7** was assigned the constitution as 2-*t*-butyl-4-propanoyloxyphenol (**17**) on the basis of its ^{1}H NMR spectral data as only one proton which appeared as a doublet (J=8Hz) moved upfield as compared to the chemical shift values of the three aromatic protons of the starting dipropanoate **7**[13] indicating that deacylation on **7** has occurred at the position *ortho* to the *t*-butyl group. The alternative structure for the product, i.e. 3-*t*-butyl-4-propanoyloxyphenol (**18**) should have shown two aromatic protons moved upfield as compared to the starting dipropanoate **7** as in it only one proton *ortho* to the acyloxy function is present. Similarly the structure of the product of deacylation reaction on compound **8**, i.e. 3,5-dimethoxy-4-propanoyloxyphenol (**19**) was arrived at on the basis of its ^{1}H NMR spectral data. The two aromatic protons moved upfield by 0.5 ppm in **19** as compared to the ones in **8** which indicated the presence of a hydroxyl group at *ortho* position with respect to the two aromatic protons. The alternative structure, i.e. 2,6-dimethoxy-4-propanoyloxyphenol (**20**) for the product was ruled out as in this case the two aromatic protons would not have moved upfield as these would have still been *ortho* to the propanoyloxy function. It is interesting to note that the alkyl groups, methyl and *t*-butyl in compounds **5**, **6** and **7** direct the deacylation at positions *ortho* to the alkyl group to give the compounds **13**, **14** and **17**, respectively, while the oxygenated function (-OCH_3 group) in compound **8** directs deacylation at position *meta* to the methoxy group to give compound **19**. From these preliminary results, it can be inferred that the lipase PPL in MBGs medium has different pockets to accommodate the alkyl and alkoxy groups.

General reaction procedure: The perpropanoate of the polyphenolic compound (500 mg) was dissolved in dry benzene (20 ml) and pelleted MBGs (415g)[12] added to it. The reaction mixture was left at 28-30°C and the progress of reaction was monitored periodically by TLC. After completion of reaction (2-4 hrs for 50-80% conversion), gel was removed by filteration, solvent removed under reduced pressure and the resulting residue purified by repeated column chromatography or preparative TLC, followed by crystallization.

These investigations which are being extended in our Laboratory are aimed to exploit the use of lipases in non-conventional media to hydrolyse selectively only one ester group derived from phenolic hydroxy groups, out of two or three such groups. This is not viable otherwise with such an ease. It may be noted that the partially acylated compounds like **9-14**, **17** and **19** are difficult to prepare in good yields by purely chemical methods and these compounds may find applications as building blocks in organic synthesis.

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10. Lipase from porcine pancreas (PPL, Type-II) was purchased from Sigma Chemical Co (USA).

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12. Microemulsions containing lipase were prepared by stirring a mixture of PPL (0.25g) and reverse micellar solution of isooctane-water - AOT [sodium *bis*-(2-ethylhexyl) sulphosuccinate], which in turn was prepared by shaking a mixture of water (4ml), isooctane (25ml) and AOT (4.9 g). Gelatin (7g) was dissolved in water (10ml) preheated to 50°C and the above microemulsion containing enzyme was added to it with shaking while maintaining the temperature a little above 50°C, the gel transition temperature. The resulting microemulsion-based gels (MBGs) were subsequently cooled to room temperature and pelleted prior to use.

13. ***Physical and spectral data of compounds*** **1-14**, **17** and **19** (the peaks for the -CH_2CH_3 groups in the ^{1}H NMR spectra of all the sixteen compounds exhibited the characteristic *J* values; from the EIMS and IR spectral data of these compounds, only the prominent and characteristic peaks are included). **1**: viscous oil; IR (neat): 1780(>C=O) cm^{-1}; MS(EI) *m/z* (%): 222(M^+)(7), 166(M^+-$COCHCH_3$)(28), 110(M^+-2x$COCHCH_3$)(92), 57($CH_3CH_2CO^+$)(100); ^{1}H NMR ($CDCl_3$): δ 1.4(t,6H,2x$OCOCH_2\mathit{CH}_3$), 2.6(q,4H, 2x$OCO\mathit{CH}_2CH_3$), 7.1-7.4(m,4H, H-3, H-4, H-5, H-6); **2**: viscous oil; IR (neat): 1780 (>C=O) cm^{-1}; MS(EI) *m/z* (%): 222(M^+)(7), 166(M^+-$COCHCH_3$)(28), 110(M^+-2x$COCHCH_3$)(100), 57($CH_3CH_2CO^+$)(64); ^{1}H NMR ($CDCl_3$): δ 1.3(t,6H, 2x$OCOCH_2\mathit{CH}_3$), 2.5(q, 4H, 2x$OCO\mathit{CH}_2CH_3$), 6.6-7.2(m,4H,H-2, H-4, H-5, H-6); **3**: white solid, m.p. 110°C (lit[14] mp 111°C); IR (Nujol): 1770(>C=O) cm^{-1}; MS(EI) *m/z* (%):222(M^+)(4), 166(M^+-$COCHCH_3$)(23), 110(M^+-2x$COCHCH_3$)(100), 57($CH_3CH_2CO^+$)(32); ^{1}H NMR ($CDCl_3$): δ 1.3(t,6H, 2x$OCOCH_2\mathit{CH}_3$), 2.5(q,4H, 2x$OCO\mathit{CH}_2CH_3$), 7.0(s,4H, H-2, H-3, H-5, H-6); **4**: viscous oil; IR(neat): 1770(>C=O) cm^{-1}; MS(EI) *m/z* (%): 294(M^+)(8), 238(M^+-$COCHCH_3$)(27), 182(M^+-2x$COCHCH_3$)(62), 126(M^+-3x$COCHCH_3$)(100), 57($CH_3CH_2CO^+$)(75); ^{1}H NMR ($CDCl_3$): δ 1.3(t, 9H, 3x$OCOCH_2\mathit{CH}_3$), 2.5(q, 6H,3x$OCO\mathit{CH}_2CH_3$), 6.8(s,3H, H-2, H-4, H-6); **5**: viscous oil; IR(neat): 1770(>C=O) cm^{-1}; MS(EI) *m/z* (%):236(M^+)(10), 180(M^+-$COCHCH_3$)(20), 124(M^+-2x$COCHCH_3$)(100), 57($CH_3CH_2CO^+$)(95); ^{1}H NMR ($CDCl_3$): δ 1.2(t, 6H, 2x$OCOCH_2\mathit{CH}_3$), 1.8(s, 3H, Ar-CH_3), 2.5(q, 4H,2x$OCO\mathit{CH}_2CH_3$), 6.8-7.2(m,3H, H-3, H-4, H-5); **6**: viscous oil; IR(neat): 1770(>C=O) cm^{-1}; MS(EI) *m/z* (%):237(M^++1)(6), 181([M^++1]-$COCHCH_3$)(7), 152(M^+-$COCHCH_3$-CO)(55), 137(M^+-$COCHCH_3$-CO-CH_3)(100), 57($CH_3CH_2CO^+$)(95); ^{1}H NMR ($CDCl_3$): δ 1.2(t, 6H, 2x$OCOCH_2\mathit{CH}_3$), 2.5-2.8(m, 7H,2x$OCO\mathit{CH}_2CH_3$,Ar-CH_3), 7.0(d, *J*=2Hz, 1H, H-3), 7.1(dd, *J*=2 and 8Hz, 1H, H-5), 7.85(d, *J*=8Hz, 1H, H-6); **7**: white solid, m.p.38°C; IR(Nujol): 1770(>C=O) cm^{-1}; MS(EI) *m/z* (%):278(M^+)(8), 222(M^+-$COCHCH_3$)(30), 166(M^+-2x$COCHCH_3$)(100), 151(M^+-2x$COCHCH_3$-CH_3)(82), 123(M^+-2x$COCHCH_3$-CH_3-CO)(22), 57($CH_3CH_2CO^+$)(95); ^{1}H NMR ($CDCl_3$): δ 1.0-1.4(m, 15H, 5xCH_3), 2.6(q, 4H,2x$OCO\mathit{CH}_2CH_3$), 6.9-7.2(m,3H, H-3, H-5, H-6); **8**:white solid, m.p.78°C; IR(Nujol): 1780(>C=O) cm^{-1}; MS(EI) *m/z*(%): 282(M^+)(37), 226(M^+-$COCHCH_3$)(97), 170(M^+-2x$COCHCH_3$)(100), 155(M^+-2x$COCHCH_3$-CH_3)(30), 127(M^+-2x$COCHCH_3$-CH_3-CO)(23), 57($CH_3CH_2CO^+$)(95); ^{1}H NMR ($CDCl_3$): δ 1.3(t, 6H, 2x$OCOCH_2\mathit{CH}_3$), 2.5(q, 4H,2x$OCO\mathit{CH}_2CH_3$), 3.7(s,6H, 2xOCH_3), 6.3(s,2H,H-3, H-5); **9**: viscous oil; IR(neat): 3450(OH), 1750(>C=O)cm^{-1}; MS(EI) *m/z* (%):166(M^+)(10), 149(M^+-OH)(7), 110(M^+-$COCHCH_3$)(78), 57($CH_3CH_2CO^+$)(100); ^{1}H NMR ($CDCl_3$): δ 1.3(t, 3H, $OCOCH_2\mathit{CH}_3$), 2.6(q, 2H,$OCO\mathit{CH}_2CH_3$), 5.7(brs, 1H, Ar-OH), 6.7-6.9(m,4H, H-3, H-4, H-5, H-6); **10**: viscous oil; IR(neat): 3420(OH), 1760(>C=O) cm^{-1}; MS(EI) *m/z*(%): 166(M^+)(16), 149(M^+-OH)(11), 110(M^+-$COCHCH_3$)(100), 57($CH_3CH_2CO^+$)(49); ^{1}H NMR ($CDCl_3$): δ 1.3(t, 3H,$OCOCH_2\mathit{CH}_3$), 2.5(q, 2H,$OCO\mathit{CH}_2CH_3$), 5.9(brs, 1H,Ar-OH), 6.3-6.9 (m,4H, H-2, H-4, H-5, H-6); **11**: white solid, m.p.77°C; IR(Nujol): 3420(OH), 1780(>C=O)

$\mathrm{cm^{-1}}$; MS(EI) *m/z* (%):166(M^{+})(11), 110(M^{+}-$\mathrm{COCHCH_3}$)(100), 57($\mathrm{CH_3CH_2CO^{+}}$)(17); ^{1}H NMR ($\mathrm{CDCl_3}$): δ 1.3(t, 3H,$\mathrm{OCOCH_2}\mathit{CH_3}$), 2.5(q, 2H, $\mathrm{OCOC}\mathit{H_2}\mathrm{CH_3}$), 5.1(s, 1H,Ar-OH), 6.6-6.8(m,4H, H-2, H-3, H-5, H-6); **12**: brown solid, m.p.95°C; IR(Nujol): 3430(OH), 1780(>C=O)$\mathrm{cm^{-1}}$; MS(EI) *m/z*(%): 238(M^{+})(8), 182(M^{+}-$\mathrm{COCHCH_3}$)(15), 126(M^{+}-2x$\mathrm{COCHCH_3}$)(100), 57($\mathrm{CH_3CH_2CO^{+}}$)(98); ^{1}H NMR ($\mathrm{CDCl_3}$): δ 1.3(t, 6H, 2x$\mathrm{OCOCH_2}\mathit{CH_3}$), 2.6(q, 4H,2x$\mathrm{OCOC}\mathit{H_2}\mathrm{CH_3}$), 3.1(brs,1H, Ar-OH), 6.5-6.7(m,3H, H-2, H-4, H-6); **13**: viscous oil; IR(neat): 3450(OH), 1750(>C=O)$\mathrm{cm^{-1}}$; MS(EI) *m/z*(%): 180(M^{+})(18), 124(M^{+}-$\mathrm{COCHCH_3}$)(100), 57($\mathrm{CH_3CH_2CO^{+}}$)(32); ^{1}H NMR ($\mathrm{CDCl_3}$): δ 1.3(t, 3H, $\mathrm{OCOCH_2}\mathit{CH_3}$), 2.0(s,3H, Ar-$\mathrm{CH_3}$), 2.6(q,2H,$\mathrm{OCOC}\mathit{H_2}\mathrm{CH_3}$), 3.6(brs, 1H,Ar-OH), 6.5-7.2(m,3H,H-3, H-4, H-5); **14**: viscous oil; IR(Nujol): 3250(OH), 1780(>C=O) $\mathrm{cm^{-1}}$; MS(EI) *m/z*(%): 180(M^{+})(12), 152(M^{+}-CO)(70), 137(M^{+}-CO-$\mathrm{CH_3}$)(100), 124(M^{+}-$\mathrm{COCHCH_3}$)(37), 57($\mathrm{CH_3CH_2CO^{+}}$)(52); ^{1}H NMR ($\mathrm{CDCl_3}$): δ 1.3(t, 3H, $\mathrm{OCOCH_2}\mathit{CH_3}$), 2.6(m, 5H, $\mathrm{OCOC}\mathit{H_2}\mathrm{CH_3}$, Ar-$\mathrm{CH_3}$), 3.0(brs,1H, Ar-OH), 6.3(d, J=2Hz, 1H, H-3), 7.0(dd, J=2 and 8Hz, 1H, H-5), 7.9(d, J=8Hz, 1H, H-6); **17**: viscous oil; IR(neat): 3450(OH), 1750(>C=O) $\mathrm{cm^{-1}}$; MS(EI) *m/z*(%): 222(M^{+})(2), 166(M^{+}-$\mathrm{COCHCH_3}$)(32), 151(M^{+}-$\mathrm{COCHCH_3}$-$\mathrm{CH_3}$)(37), 123(M^{+}-$\mathrm{COCHCH_3}$-$\mathrm{CH_3}$-CO)(33), 57($\mathrm{CH_3CH_2CO^{+}}$)(100); ^{1}H NMR ($\mathrm{CDCl_3}$): δ 1.0-1.4(m, 12H, 4x$\mathrm{CH_3}$), 2.4(brs, 1H, Ar-OH), 2.6(q, 2H,$\mathrm{OCOC}\mathit{H_2}\mathrm{CH_3}$), 6.2(d, J=8Hz, 1H, H-6), 6.9-7.1(m, 2H, H-3, H-5). **19**: semi-solid; IR(neat): 3500(OH), 1760(>C=O)$\mathrm{cm^{-1}}$; MS(EI) *m/z*(%): 227(M^{+}+1)(3), 170(M^{+}-$\mathrm{COCHCH_3}$)(69), 155(M^{+}-$\mathrm{COCHCH_3}$-$\mathrm{CH_3}$)(27), 127(M^{+}-$\mathrm{COCHCH_3}$-$\mathrm{CH_3}$-CO)(47), 57($\mathrm{CH_3CH_2CO^{+}}$)(100); ^{1}H NMR ($\mathrm{CDCl_3}$): δ 1.3(t, 3H, $\mathrm{OCOCH_2}\mathit{CH_3}$), 2.5(q, 2H,$\mathrm{OCOC}\mathit{H_2}\mathrm{CH_3}$), 3.4(brs, 1H, Ar-OH), 3.6(s,6H, 2x$\mathrm{OCH_3}$), 5.8(s,2H, H-2, H-6).

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16. The isolated yields of the products are much lower than the % of conversions of the substrates as it was quite difficult to remove gelatin from the reaction mixtures and several chromatographic operations had to be performed, followed by prep TLC/ crystallization to isolate the products in the pure form, we have not recovered the substrates. No by-product was observed to be formed during the course of these reactions.

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