Use of Highly Cross-Linked Polystyrene Supports for Acylation and Alkylation of an Ester Enolate at Room Temperature[1]

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The enolate of polystyrene-bound 3-phenylpropanoic ester is prepared with (triphenylmethyl)lithium in tetrahydrofuran at room temperature and is trapped with carboxylic acid chlorides and alkyl bromides. Gas chromatographic yields exceed 90%, and isolated yields are 73–87% with a partially esterified 10% divinylbenzene-cross-linked gel copolymer containing 0.67 mmol of ester/g of copolymer. Yields of *p*-nitrobenzoylation and self-condensation depend upon the degree of cross-linking of the polystyrene support, the gel or macroporous morphology of the polymer, the degree of functionalization of the polymer, the percent conversion of the chloromethyl polystyrene to ester, the structure of the base used to form the enolate, the time between enolate generation and trapping with *p*-nitrobenzoyl chloride, and the temperature. Yields of acylation product increase, and self-condensation of the ester decreases as percent cross-linking increases from 2% to 20% and as the concentration of ester in fully esterified polymers decreases from 1.08 to 0.18 mmol/g of polymer. When the original esterification of the polymer is carried to only partial conversion, the subsequent enolate acylation yields increase, conversion, the subsequent enolate acylation yields increase, self-condensation yields decrease, and unreacted ester yields decrease. Macroporous 20% cross-linked polymers gave better site isolation than 10% cross-linked gel polymers but lacked the physical stability necessary for recycling. One sample of 10% cross-linked gel polymer in three esterification/enolate acylation/hydrolysis cycles showed no decrease in acylation yield but a decrease in the degree of functionalization. The higher degrees of cross-linking and functionalization of the polystyrene in this work than in similar experiments with a conventional 2% cross-linked polystyrene enable ester enolate acylation in 77% yield at room temperature on a 0.1-mol scale in just 1400 mL of reaction mixture.

Insoluble polymer supports for reagents and catalysts in organic synthesis enable separation of the polymer-bound species from all other components of a reaction mixture by filtration.[2] In spite of this great advantage, polymer supports have been used extensively only for solid-phase peptide synthesis.[3] They are not yet common in organic synthetic methodology. We believe that the almost exclusive use of 1–4% divinylbenzene-cross-linked polystyrenes as the polymer supports has retarded development of solid-phase synthesis because the properties of those polymers are not well suited for many synthetic applications. Their high swellability limits the scale of syntheses that can be performed and often does not immobilize reactive species in the polymer matrix. This paper describes how more highly cross-linked polystyrene supports enable high-yield ester enolate syntheses at room temperature on a large scale. Normally in solution ester enolates are generated at −78 °C to prevent self-condensation of the ester.[4]

There are many conflicting reports about the ability of polymer supports to provide "site isolation" of reactive polymer-bound species.[5] The aim of site-isolation syntheses is to prevent reaction of two polymer-bound species with one another and thereby promote reaction of the polymer-bound species with a reagent in solution or intramolecular reaction of the polymer-bound species. The polymer-polymer reactions can be prevented only if the network is rigid enough to isolate reactive sites from one another. Intrapolymer formations of anhydrides,[6] organocobalt dimers,[7] and disulfides[8] and homologation of α,ω-diiodoalkanes[9] demonstrate that the common 1–4% divinylbenzene-cross-linked polystyrene supports cannot isolate reactive species from one another over periods of hours. ESR relaxation times of polystyrene-bound nitroxyl radicals[10] and ^{13}C NMR relaxation times of cross-linked polystyrenes[11] also demonstrate considerable mobility of the polymer chains in solvent-swollen gels. Lifetimes of a few minutes have been determined for dimerization of polymer-bound benzyne[12] on 2% and 20% cross-linked polystyrene and for polymer–polymer reactions of amines and active esters[13] on 4% cross-linked polystyrene. Site isolation also plays an important role in the activity of polymer-bound transition-metal catalysts.[5f-h] Site isolation is a matter of timing. Synthetic reactions that normally proceed "instantaneously" in solution are slower when both reactants are polymer bound, but the polymer network is

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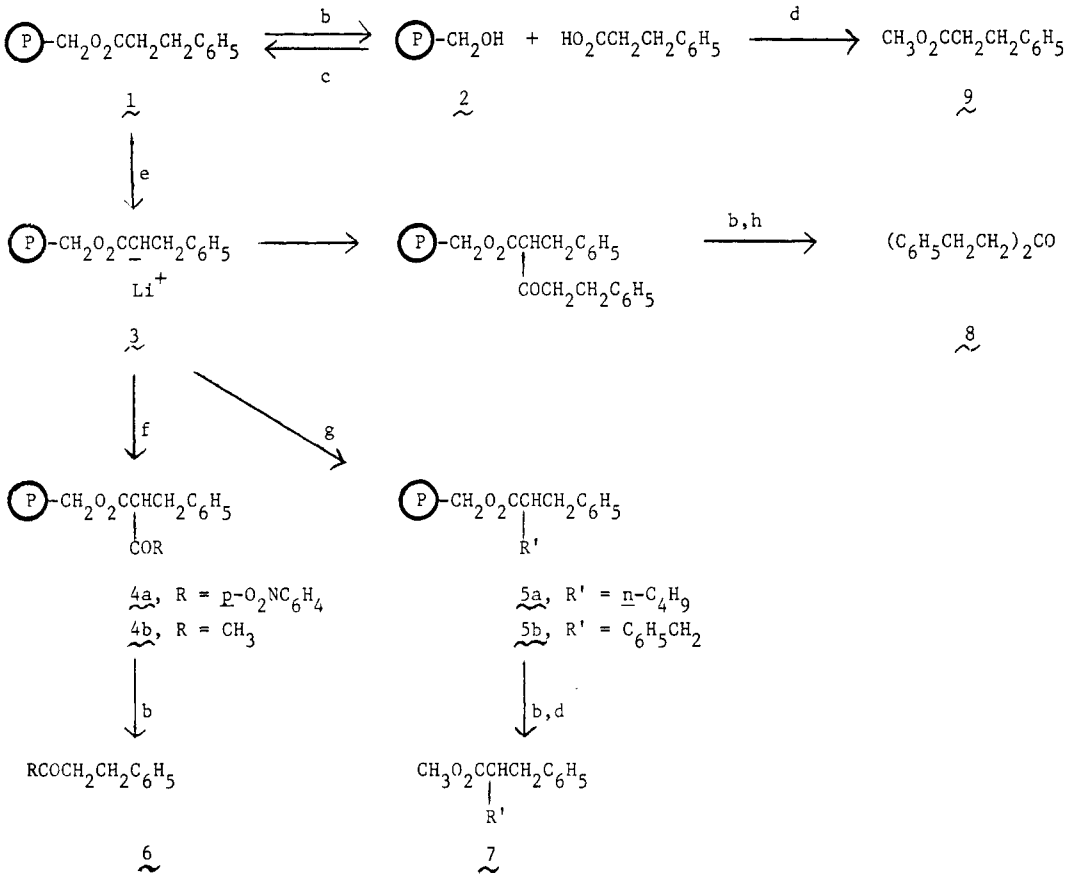
0022-3263/81/1946-5364$01.25/0

Scheme I[a]



[a] P = *m*- or *p*-polystyryl. (b) i, KOH, $(n\text{-}C_4H_9)_4NOH$, THF, 75 °C; ii, HCl. (c) i, $(C_6H_5)_3CLi$, THF; ii, $ClCOCH_2CH_2C_6H_5$. (d) CH_2N_2. (e) $(C_6H_5)_3CLi$, THF, 25 °C. (f) RCOCl, THF. (g) RBr, THF. (h) HCl, reflux.

not rigid enough to prevent polymer–polymer reactions over long periods of time.

At the center of the controversy over whether polymer supports can provide useful site-isolation syntheses are Kraus and Patchornik,[14] who reported acylation and alkylation of polymer-bound ester enolates in low yields at 0–25 °C without self-condensation of the ester, and Crowley and Rapoport,[5d,e] who failed in heroic attempts to achieve Dieckmann cyclization of polymer-bound diesters to nine-membered rings and carried out detailed radiolabeling studies to determine the actual reaction pathways of the diesters. All of the Kraus and Patchornik and the Crowley and Rapoport experiments were carried out with highly flexible, 2–4% cross-linked polystyrenes. Both groups reduced the loading of polymer-bound species to 0.10 mmol of ester/g of dry polymer in their attempts to prevent polymer–polymer reactions, but neither attempted to reduce polymer chain mobility by use of more highly cross-linked polymers or by carrying out reactions in nonswelling solvents. We report here that ester enolates can be generated and trapped at room temperature in high yields by using 10–20% cross-linked polystyrenes and degrees of functionalization as high as 0.67 mmol/g.

Results

Scheme I summarizes the polymer-bound ester enolate syntheses. The polymer in all cases is a divinylbenzene-cross-linked copolymer of styrene and chloromethylstyrene (60/40 meta/para) prepared by suspension techniques in our own laboratory. This method of polymer preparation offers major advantages over chloromethylation of cross-linked polystyrene with a Lewis acid catalyst: (1) It avoids the use of the cancer suspect agent chloromethyl methyl ether. (2) The degree of functionalization of the polymer is established by the composition of the monomer mixture, because polymerization is carried essentially to completion. Chloromethylation requires trial-and-error determination of the conditions required to reach a certain degree of functionalization. (3) The rigidity of the polymer matrix can be varied readily by varying the divinylbenzene content of the copolymer.

Both gel and macroporous have been prepared. The only difference in their syntheses is that an inert diluent is used for macroporous polymers to effect precipitation of polymer during the polymerization.[15] The macroporous polymer consists of porous spheres with diluent in the pores. The diluent is removed by steam distillation.

Polymer-Bound 3-Phenylpropanoic Ester. Complete esterification is attained by heating a fivefold excess of potassium 3-phenylpropanoate, a phase-transfer catalyst,[16] and the (chloromethyl)polystyrene in *o*-dichlorobenzene at 95 °C for 4 days. This procedure gives polymer-bound ester with no residual chlorine by elemental analysis and strong infrared absorption at 1730 and 1235 cm^{-1}, char-

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Table I. Polymer-Bound 3-Phenylpropanoic Esters 1

copolymer[a]	mmol of Cl/g in copolymer: monomer compd	mmol of Cl/g in copolymer: elemental anal.	mmol of ester/g: found	mmol of ester/g: theor[b]
G2	0.20	0.16	0.15	0.20
G2	0.60	0.73	0.71	0.56
G6	0.70	0.77	0.64	0.65
M4	1.50	1.51	1.05	1.28[c]
M6	1.60	1.54	1.18	1.35[d]
M20	0.24	0.38	0.18	0.23
M20	0.60	*e*	0.55	0.56
M20	1.00	1.10	1.08	0.88

[a] G2 = gel copolymer, −200 + 400 mesh, containing 4% DVB; G6, M6, and M20 are denoted similarly. The weight percent of DVB in the copolymer mixture is based on 55% active component in technical grade DVB. [b] Based on Cl content of monomer mix. In some cases calculation based on the elemental analysis would give better agreement with experiment. [c] Product also contained 0.30 mmol of Cl/g. [d] Product also contained 0.20 mmol of Cl/g. [e] Not determined.

acteristic of carbon–oxygen double and single bonds.

The degree of functionalization of the polymer-bound ester was determined by complete saponification with potassium hydroxide and tetra-*n*-butylammonium hydroxide catalyst in boiling aqueous tetrahydrofuran (THF) at 75 °C for 24 h. Recovered 3-phenylpropanoic acid was esterified to **9** with diazomethane and analyzed by gas chromatography. Recovered polymer **2** showed no 1730-cm^{-1} absorption in its infrared spectrum. Analytical data for typical chloromethyl polymers and polymer-bound esters are in Table I. The chlorine contents of the copolymers determined from the original monomer composition and from elemental analysis differ by up to 0.14 mmol of Cl/g of dry polymer, which corresponds with a 0.5 wt % Cl error in elemental analysis. Since copolymer reactivity ratios show that styrene and (chloromethyl)-styrenes form nearly random copolymers[17] and the polymerizations were carried to essentially complete conversion, the monomer composition provides a more accurate determination than elemental analysis of the chlorine content and is used to calculate theoretical yields in Table I. However, in some cases use of the chlorine content of the copolymer found by elemental analysis would give better agreement between theoretical and experimental ester contents.

After development of the method for complete esterification, some chloromethyl polymers were allowed to react with potassium 3-phenylpropanoate for shorter times to afford partially esterified polymers containing residual chloromethyl groups. Results in Table II show that 4 days actually are needed for complete esterification. The theoretical and experimental ester contents reported in Table II after 4-day reactions agree to within 0.04 mmol ester/g of polymer for four polymers that differ in morphology, cross-linking, and degree of functionalization.

Generation and Trapping of Ester Enolates. Triphenylmethyllithium (1.5 molar equiv in THF) was used to generate the enolate of polymer-bound 3-phenylpropanoic esters **3**. The fading of its red color serves as an indicator that the base has penetrated the polymer and converted ester to enolate. Kraus and Patchornik[14c] used the same base in benzene/1,2-dimethoxyethane. The

(17) Copolymer reactivity ratios for chloromethylstyrenes (m_1) and styrene (m_2) are r_1 = 1.08 and r_2 = 0.72 at 60 °C: Young, L. J. In "Polymer Handbook", 2nd ed.; Brandrup, J., Immergut, E. H., Eds.; Wiley-Interscience: New York, 1975; pp 11-344.

Table II. Partial Esterification of (Chloromethyl)polystyrenes

copolymer[a]	mmol of Cl/g[b]	reaction time, days	mmol of ester/g	% ester[c]
M20	1.10	1	0.46	44
		2	0.76	76
		3	0.89	90
		4	0.98	100
M20	0.55	1	0.24	45
		2	0.37	70
		3	0.47	90
		4	0.53	103
G6	1.00	1	0.39	41
		2	0.68	74
		3	0.81	89
		4	0.86	95
G6	2.00	1	0.94	53
		2	1.37	81
		3	1.56	95
		4	1.67	103
G10	2.00	0.5	0.41	22
		1.0	0.68	37
		1.5	0.87	48
		2.0	1.12	64

[a] See footnote *a* in Table I. [b] Based on Cl content of monomer mix. [c] Percent ester = $100P/S(1 - PW)$ where P = milliequivalents of ester/gram of polymer-bound ester, S = mmol of Cl/gram of chloromethyl polymer, and W = weight gain per milliequivalent of ester = 0.1135 g/mequiv of ester.

Table III. *p*-Nitrobenzoylation of Fully Esterified Polystyrenes 1 as Functions of Morphology, Cross-Linking, and Degree of Functionalization

polymer[a]	[ester], mmol/g	% yield[b]: acylation, **6a**	% yield[b]: self-condensation, **8**	% yield[b]: unreacted **9**
G2	0.15	44	21	33
G2	0.71	24	40	33
G6	0.64	46	16	34
M4	1.05	26	40	33
M6	1.18	27	38	33
M20	0.18	56	0	44
M20	0.55	55	0	44
M20	1.08	42	17	39

[a] See footnote *a* in Table I. [b] Determined by GC.

electrophilic acyl chloride or alkyl bromide (2.0 molar equiv) was added as soon as the color faded, usually after about 1 min at room temperature with vigorous stirring. To survey the effects of polymer morphology and cross-linking on the yields of enolate acylation and self-condensation, *p*-nitrobenzoyl chloride was used as the standard electrophile. After acylation the polymer (**4a**) was filtered and washed thoroughly to remove excess reagents and possible byproducts. The mixture of polymer-bound esters was saponified by the same method used for analysis of polymer-bound ester **1**. The hydrolysate was acidified and heated to decarboxylate the acylation and self-condensation products to ketones **6a** and **8**, and the resulting mixture was treated with diazomethane to esterify recovered 3-phenylpropanoic acid to **9** for GC analysis. Yields of mixtures of **6a**, **8**, and **9** obtained from a variety of fully esterified polymers **1** are in Table III. Several trends in the data are important. (1) With 2% cross-linked gel polymer and with 20% cross-linked macroporous polymer the acylation yield decreases and the self-condensation yield increases as the concentration of ester bound to the polymer increases. The experiment in Table

Table IV. Effects of Base, Time, and Temperature on *p*-Nitrobenzoylation of Polymer-Bound 3-Phenylpropanoic Ester 1[a]

[ester], mmol/g	base	temp, °C	time,[b] min	% yield[c] acylation, 6a	% yield[c] self-condensation, 8	% yield[c] unreacted 9
0.18	Ph_3CLi	20–25	1	56	0	44
1.08	Ph_3CLi	20–25	1	42	17	39
1.08	Ph_3CLi	−10	10	61	0	39
0.18	*i*-Pr_2NLi	20–25	1	59	18	21
1.08	*i*-Pr_2NLi	20–25	1	38	38	22
1.08	*i*-Pr_2NLi	20–25	10	1	79	20
1.08	*i*-Pr_2NLi	−10	1	38	39	25
1 08	*i*-Pr_2NLi	−10	10	44	39	15

[a] −60 + 100-mesh, macroporous, 20% divinylbenzene-cross-linked polymer. [b] Time between addition of base and addition of *p*-nitrobenzoyl chloride. [c] Determined by GC.

III with 2% cross-linked gel polymer loaded with 0.15 mmol of ester/g of polymer is comparable to a Kraus and Patchornik experiment[14c] in which 25% acylation and 1% self-condensation were observed by carrying out enolate formation and acylation at 0 °C rather than at 20–25 °C. (2) Increasing the cross-linking level of the gel polymer from 2% to 6% or of the macroporous polymer from 6% to 20% increases the acylation yield and decreases the self-condensation yield. (3) No self-condensation is detected with the 20% cross-linked macroporous polymer at an ester concentration of 0.55 mmol/g of polymer, and only 17% self-condensation occurs at 1.08 mmol of ester/g of polymer. (4) In all experiments with fully esterified polymers 33–44% of the polymer-bound ester failed to react.

A stronger base, lithium diisopropylamide (LDA), was used to try to reduce further the yield of self-condensation (see Table IV). The key results are: (1) LDA gave more self-condensation than triphenylmethyllithium under three different sets of conditions. (2) At room temperature LDA gave less unreacted polymer-bound ester. The acylation yields from 1-min reactions with LDA and with triphenylmethyllithium before addition of *p*-nitrobenzoyl chloride were almost the same. (3) Longer treatment with LDA at room temperature gave only self-condensation and unreacted ester. (4) Decreasing the temperature from ambient to −10 °C had no effect on 1-min LDA reactions. The lower temperature increased acylation and decreased self-condensation in 10-min reactions. (5) At −10 °C with 10 min between addition of triphenylmethyllithium and addition of *p*-nitrobenzoyl chloride, no self-condensation occurred even with a high degree of functionalization, 1.08 mmol of ester/g of polymer.

Partial esterification of the (chloromethyl)polystyrenes provided high acylation yields with no self-condensation at room temperature. Table V shows how the yields with five different copolymers depend on degree of esterification. With 6% cross-linked gel polymers triphenylmethyllithium always gave some self-condensation. As the degree of esterification increases, acylation yields decrease, and both self-condensation and unreacted ester yields increase. Figure 1 shows that acylation yields of ≥90% were attained only when <50% of the chloromethyl groups in starting copolymer were converted to ester. With the 6% and 10% cross-linked gel polymers, the decreased acylation yields at higher percent ester loading are due to nearly equal amounts of self-condensation and unreacted ester. With the 20% cross-linked macroporous polymer, the decreased acylation yields at higher percent ester loading are due mainly to unreacted ester.

After polymers had been found that minimize self-condensation in competition with acylation by the highly reactive *p*-nitrobenzoyl chloride, the polymer-bound enolate was trapped with the less reactive electrophiles acetyl chloride, benzyl bromide, and 1-bromobutane. Results are in Table VI. All four electrophiles gave high GC yields, no self-condensation, and a trace of unreacted ester on

Table V. Effect of Partial Esterification of (Chloromethyl)polystyrene on *p*-Nitrobenzoylation of 3-Phenylpropanoic Ester 1[a]

polymer[b]	mmol of Cl/g[c]	[ester], mmol/g	% yield[d] acyl-	% yield[d] self-condensation, 8	% yield[d] unreacted 9
G6	1.00	0.39	81	10	6
		0.68	52	17	27
		0.81	30	30	38
G6	2.00	0.94	78	19	0
		1.37	50	24	24
		1.56	23	38	37
G10	2.00	0.41	96	0	0
		0.68	90	0	6
		0.97	75	10	11
		1.12	64	14	18
M20	0.55	0.24	100	0	0
		0.37	81	0	18
		0.53	59	0	41
M20	1.10	0.46	99	0	0
		0.76	66	10	24
		0.98	43	17	38

[a] All reaction were performed at room temperature by addition of 1.5 molar equiv of triphenylmethyllithium to the polymer in THF and addition of 2.0 molar equiv of *p*-nitrobenzoyl chloride after 1 min. [b] See footnote *a* in Table.I. [c] Based on composition of monomers. [d] Determined by GC.

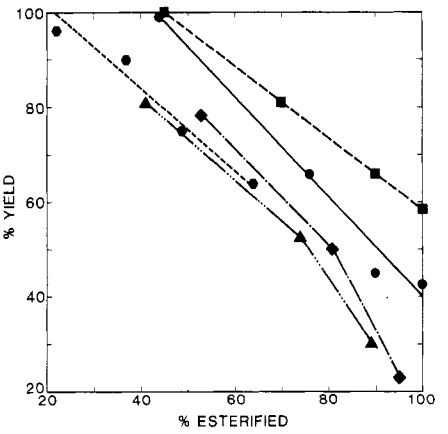

Figure 1.

Table VI. Acylations and Alkylations of Polymer-Bound Enolate 3 of 3-Phenylpropanoic Ester[a]

		% yield[c]					% yield[c]		
polymer[b]	electrophile	acyl or alkyl product 6 or 7	self-condensation, 8	unreacted 9	polymer[b]	electrophile	acyl or alkyl product 6 or 7	self-condensation, 8	unreacted 9
M20	p-$O_2NC_6H_4COCl$	42	17	39	G10	p-$O_2NC_6H_4COCl$	94	0	5
	CH_3COCl	57	7	36		CH_3COCl	95	0	4
	n-C_4H_9Br	63	1	36		n-C_4H_9Br	97	0	2
	$C_6H_5CH_2Br$	59	3	37		$C_6H_5CH_2Br$	95	0	4

[a] For conditions see footnote a in Table V. [b] See footnote a in Table I. [c] Determined by GC.

Table VII. Isolated Yields from Acylation and Alkylation of Polymer-Bound Enolate 3 of 3-Phenylpropanoic Ester[a]

polymer[b]	electrophile	mmol of ester	% yield
G10	p-$O_2NC_6H_4COCl$	27.4	85
G10	p-$O_2NC_6H_4COCl$	103.2	77
M20	p-$O_2NC_6H_4COCl$	50.3	40
G10	CH_3COCl	17.2	87
G10	n-C_4H_9Br	17.6	80
G10	n-C_4H_9Br	34.4	78
G10	$C_6H_5CH_2Br$	15.8	73
G10	$C_6H_5CH_2Br$	31.6	74

[a] Reaction conditions are in footnote a of Table V. [b] See footnote a in Table I. The polymer M20 was fully esterified. The polymer G10 contained 36% ester and 64% residual chloromethyl groups from an original copolymer that had 2.00 mmol of Cl/g, except in the 103.2-mmol experiment in which G10 contained 32% ester and 68% residual chloromethyl groups.

Table VIII. Recycling of Polymer for p-Nitrobenzoylation of Polymer-Bound 3-Phenylpropanoic Ester 1[a]

			% yield[b]	
cycle	[ester], mmol/g	wt of polymer, g	acylation, 6a	unreacted 9
1	0.67	40.00	87	3
2	0.42	36.67	88	4
3	0.39	32.11	90	6

[a] Prepared from 10% cross-linked gel polymer containing 2.00 mmol of Cl/g. Reaction conditions are in footnote a of Table V. [b] Yields of 6a in cycles 1 and 2 are isolated. Yield of 6a in cycle 3 and all yields of 8 and 9 were determined by GC. No 8 was found in any case.

using a 36% esterified, 10% cross-linked gel polymer as the starting material. p-Nitrobenzoyl chloride gave more self-condensation than the other electrophiles, 17% vs. 1–7% for the others, and all four electrophiles left 36–39% unreacted ester when the starting material was a fully esterified (1.08 mmol of ester/g of polymer) 20% cross-linked macroporous polymer.

The high GC yield experiments were repeated on a much larger scale to obtain gram quantities of isolated products. ^1H NMR and infrared spectra of isolated products were identical with those of independently synthesized, purified materials. Results are in Table VII. All of the isolated yields were ≥73% when a 10% cross-linked gel polymer containing 36% ester and 64% residual chloromethyl groups was used.

Another potential advantage of polymer-supported synthesis is recycling of the polymer. Our choice of a polymer to recycle was dictated by physical stability. The 10% cross-linked gel polymers were recovered as whole spherical beads after hydrolysis of polymer-bound esters, while the 20% cross-linked macroporous polymers were recovered as powders that were difficult to filter. The breakdown of macroporous beads occurred with two samples having different porosities created by use of 45% and 35% by volume of 4-methyl-2-pentanol in the monomer phase during polymerization. (We had reasoned that the lesser porosity obtained with 35% diluent might make the polymer beads more stable physically.) Recovered 10% cross-linked gel polymer from a p-nitrobenzoylation experiment was washed thoroughly, dried, and converted back to 3-phenylpropanoic ester by sequential treatment with triphenylmethyllithium and 3-phenylpropanoyl chloride. This procedure gave ester contents lower than the original and small losses of polymer beads during handling. However, p-nitrobenzoylation proceeded in as high yield in the third cycle as it did in the first cycle. Results are in Table VIII.

Finally, to compare results of polymer-bound enolate generation and trapping with a similar reaction in homogeneous solution, a 0.11 M solution of benzyl 3-phenylpropanoate was treated with triphenylmethyllithium and p-nitrobenzoyl chloride just as in the polymer-supported syntheses. GC analysis of the product mixture showed 19% of the p-nitrobenzoyl product 6a, 58% of self-condensation product 8, no unreacted benzyl 3-phenylpropanoate, and small amounts of unidentified products. The concentration of ester in this control experiment was the same as the concentration of polymer-bound ester with 10% cross-linked gel polymer containing 0.67 mmol of ester/g of polymer.

Discussion

Kraus and Patchornik's[14] pioneering experiments on 2% cross-linked gel and popcorn polystyrene supports gave p-nitrobenzoylation of the enolate of 3-phenylpropanoic ester at room temperature in ≤37% yield with ≤1% self-condensation and no identification of other products. They probably also had substantial amounts of unreacted polymer-bound ester. Use of more highly cross-linked polystyrene supports improved their method in three ways: (1) Isolated yields of 73–87% were obtained with a variety of electrophiles. (2) A 4–5 times higher concentration of polymer-bound ester (0.67 mmol/g vs. 0.15 mmol/g) can be used. (3) Lesser swelling of the polymer along with the higher concentration of ester in the polymer gives a tenfold reduction in the total volume of the reaction mixture required to perform a synthesis. These combined improvements have enabled synthesis of 1-(p-nitrophenyl)-3-phenyl-1-propanone from polymer-bound 3-phenylpropanoic ester on a 0.10-mol scale in 1400 mL of reaction mixture.

Successful site-isolation syntheses require that the solvent-swollen polymer be flexible enough to permit diffusion of reactants such as triphenylmethyllithium and

electrophiles to the reaction sites in the polymer matrix but rigid enough to prevent encounter of two different polymer-bound species such as the ester enolate and neutral ester. The time scale of our experiments, 1 min between addition of strong base and addition of electrophile, is about the same as that found by Mazur and Jayalekshmy[12] to limit dimerization of polymer-bound benzyne and that found by Rebek and Trend[13] to limit intrapolymer reaction of amines with activated esters. Their experiments were performed mainly with 2–4% cross-linked polystyrenes in swelling solvents.

Table VI contains one indication of the importance of rapid diffusion of electrophile into the polymer to prevent self-condensation of the ester. The largest and presumably slowest diffusing electrophile, *p*-nitrobenzoyl chloride, gives a lower yield of acylation and a higher yield of self-condensation than do the smaller electrophiles.

Figure 1 indicates that the 20% cross-linked macroporous polymer is more effective than the 10% cross-linked gel polymer in promoting site-isolation synthesis. At every comparable degree of esterification the 20% cross-linked macroporous polymer gave the higher acylation yield. (Data in Tables III, IV, and VI might lead one to conclude that the 10% cross-linked gel polymer gives higher yields, but those data were all obtained with fully esterified 20% cross-linked macroporous polymers shown to leave large amounts of unreacted ester in most experiments.) The advantage of the gel polymer is greater physical stability. The crumbling of macroporous polymers that we observed is not unusual, but physically stable commercial macroporous ion-exchange resins and size-exclusion chromatography packings are common. Physically stable macroporous beads likely can be developed for site-isolation syntheses if more effort is made to improve the macroporous bead synthesis.

When polystyrene cross-linking reaches 20% divinylbenzene, macroporous morphology is needed to limit the time required for diffusion of a reagent from the external solution to a reactive site in the polymer matrix. Diffusivity in the matrices of gel and macroporous polymers with the same percent cross-linking should be the same, but macroporosity greatly shortens the length of the diffusion path through the matrix. The macro polymer bead (150–250-μm diameter) is composed of many fused microbeads (<1 μm in diameter) separated by macropores (<1 μm in diameter) filled with liquid phase. With macroporous polymers the longest reactant diffusion path is in the quiet liquid in the macropores rather than in the polymer matrix. Although we have not tested 20% cross-linked gel polymer beads for ester enolate acylations, we predict that times much longer than 1 min between the addition of strong base and addition of the electrophile would be required to achieve high yields. The necessity for macroporous polystyrene supports at cross-linking of >10% has been recognized by ion-exchange resin manufacturers for many years.

The chloromethyl sites in the 10% and 20% cross-linked polystyrenes must be only partly esterified to obtain high-yield ester enolate generation and trapping. Apparently the sites in the heterogeneous polymer matrix that are most readily esterified are also the sites that react in 1 min or less after addition of triphenylmethyllithium in THF. When esterification is carried to completion, some of the ester sites are in hindered positions of the polymer matrix that can be reached only slowly or not at all by triphenylmethyllithium.

What happens to the unreacted chloromethyl groups in the polymer upon treatment with triphenylmethyllithium? We presume that over a long time they would undergo either substitution or electron-transfer reduction by the triphenylmethyl carbanion. Two bits of evidence indicate that most of the residual chloromethyl groups do not react with the excess triphenylmethyllithium before it is quenched with excess acylating or alkylating agent. First, polymer recovered after hydrolysis of all of the esters still contains chlorine in spite of the long exposure to KOH in aqueous THF. Second, only a 50% excess of triphenylmethyllithium was used in all experiments. The 10% cross-linked gel polymer that gave ≥95% GC yields contained 0.67 mmol of ester/g of polymer and 1.19 mmol of chloromethyl groups/g of polymer. No more than 0.34 mmol of chloromethyl groups/g of polymer could react with triphenylmethyllithium and still permit quantitative formation of the ester enolate.

In conclusion, the high-yield room-temperature ester enolate syntheses in this paper should direct attention to use of highly cross-linked, partially functionalized polystyrenes for other site-isolation syntheses. Success of such experiments requires finding the proper delicate balance between polymer flexibility sufficient to permit diffusion of reagents to reactive sites in the matrix and insufficient to permit intrapolymer reactions between two bound species. No single polymer is well-suited for all site-isolation syntheses, just as the Merrifield resin is not well-suited for all polymer-supported syntheses. Tailoring of polymers to suit specific synthetic reactions is necessary.

Experimental Section

Elemental analyses were performed by Midwest Microlab. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-24B 60-MHz instrument at ambient probe temperature by using 10 v/v % solutions in $CDCl_3$ with 1% Me_4Si, except as noted. IR spectra were obtained with Perkin-Elmer Model 197 and Beckman Model 5A spectrophotometers. Samples of polymers (3 mg) were mixed with 300 mg of anhydrous potassium bromide in a Wig-L-Bug (Crescent Dental Mfg. Co.) for 5 min and pressed into translucent wafers, except as noted. Gas chromatographic analyses employed a Varian Aerograph Model A-90-P thermal-conductivity instrument with 0.25-in.-o.d. columns. Chromosorb Q (80/100 mesh) was used as the support. The columns employed were as follows: A, 6 ft, 5% SE-30; B, 6 ft, 10% SE-30; C, 6 ft, 15% SE-30; D, 3 ft, 10% SE-30. Quantitative GC analyses were carried out by making four injections per determination, tracing the peaks on an unlined filing card, cutting them out, and weighing them. The relative response factors of authentic samples were determined relative to *o*-dichlorobenzene internal standard ($NO_2C_6H_4COCH_2CH_2Ph$, 0.74; $PhCH_2CH_2COCH_2CH_2Ph$, 0.82; $CH_3OOCCH_2CH_2Ph$, 0.98; *o*-dichlorobenzene, 1.00). Yields were calculated from the relative peak weights of the products and *o*-dichlorobenzene.

Anhydrous diethyl ether from sealed cans (Fisher) was used immediately after the cans were opened. Tetrahydrofuran (Fisher) was dried by refluxing with $LiAlH_4$ for at least 4 h before distillation in an inert atmosphere. All other chemicals were reagent grade and were used without further purification unless specified.

Each time a polymer was isolated, it was washed routinely in a fritted Buchner funnel for a contact time of 30–60 min each with the following solvents: THF–acetone (1:1), acetone, THF–methanol (3:1), methanol–water (3:1), THF, acetone, methanol. The polymers were dried under reduced pressure at 60–80 °C overnight.

Methyl 3-phenylpropanoate was obtained by esterification of 3-phenylpropanoic acid in methanol with H_2SO_4, distilled rapidly at atmospheric pressure, and purified in small quantities by GC on column B at 270 °C or by TLC on silica gel with ethanol (R_f 0.77): ^{1}H NMR δ 2.5 (m, 4), 3.7 (s, 3), 7.4 (s, 5).

1,5-Diphenyl-3-pentanone was prepared from 1,3-dithiane and (2-bromoethyl)benzene[18] and purified on a small scale by GC

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on column B at 270 °C or by TLC on silica gel with benzene (R_f 0.64): ^{1}H NMR δ 2.7 (m, 8), 7.1 (s, 10).

1-(4-Nitrophenyl)-3-phenyl-1-propanone was prepared from di-*tert*-butyl benzylmalonate and *p*-nitrobenzoyl chloride[19] and purified on a small scale by GC on column B at 270 °C or by TLC on silica gel with benzene (R_f 0.71): ^{1}H NMR δ 3.1 (m, 4), 7.2 (s, 5), 8.1 (m, 4); mp 74–75 °C (lit.[19] mp 74.5–75 °C).

Methyl 2-benzylhexanoate was prepared by reaction of 1-bromobutane and the dilithio derivative of 3-phenylpropanoic acid[20] in THF–HMPA followed by esterification of the 2-benzylhexanoic acid in methanol with H_2SO_4. The intermediate 2-benzylhexanoic acid was purified by distillation at 127–130 °C (3 torr) [lit.[21] bp 127–130 °C (3 torr)]. The methyl ester was purified on a small scale by GC on column A at 200 °C: ^{1}H NMR δ 7.2 (s, 5), 3.6 (s, 3), 2.5–3.1 (m, 3), 0.8–1.7 (m, 9).

Methyl 2-benzyl-3-phenylpropanoate was prepared by reaction of benzyl bromide and the dilithio derivative of 3-phenylpropanoic acid[20] in THF–HMPA followed by esterification of the 2-benzyl-3-phenylpropanoic acid with methanol and H_2SO_4. The intermediate 2-benzyl-3-phenylpropanoic acid was distilled at 120–150 °C (0.2 torr) [lit.[22] bp 235 °C (18 torr)]. The methyl ester was purified by column chromatography over silica gel with diethyl ether as the eluant: ^{1}H NMR δ 7.2 (s, 10), 3.5 (s, 3), 2.6–3.2 (m, 5).

Suspension Copolymerizations. Gel polymers were prepared by a method described elsewhere;[23] only the monomer composition was varied. Sodium dodecylbenzenesulfonate was used in the polymerization mixture to obtain a high yield of the −200 + 400-mesh beads used in later experiments. Macroporous polymers were prepared by the same method except the monomer phase contained 45% by weight 4-methyl-2-pentanol (Aldrich) and no sodium dodecylbenzenesulfonate. In our macroporous sample only 35% 4-methyl-2-pentanol was used (see Results). The 4-methyl-2-pentanol was removed by steam distillation before isolation of the polymer beads. Only the −60 + 100-mesh fraction of macroporous polymers was used in subsequent experiments.

Polymer-Bound 3-Phenylpropanoic Ester. To 50 g of 2% cross-linked gel (chloromethyl)polystyrene (0.20 mmol of Cl/g of polymer) in 250 mL of *o*-dichlorobenzene were added 0.3 g of tetra-*n*-butylammonium bromide (Aldrich) and a solution of potassium 3-phenylpropanoate, prepared by heating 3-phenylpropanoic acid (7.5 g, 50 mmol) with KOH (2.8 g, 50 mmol) in 80 mL of ethanol–hexamethylphosphoramide (1:1) at 50 °C until a clear solution formed. The mixture was refluxed at 95 °C while being stirred mechanically under N_2 for 4 days. The polymer was filtered, washed, and dried: IR (KBr) 1730, 1235 cm^{-1}. The same procedure was used for all other (chloromethyl)polystyrenes.

Degree of Functionalization of Polymer-Bound Ester. A mixture of 2.00 g of dry polymer-bound ester, 5 mL of 50% aqueous KOH, 20 mL of THF, and 0.2 g of tetra-*n*-butylammonium hydroxide (40% aqueous, Aldrich) was stirred at 75 °C for 24 h. After cooling to room temperature the mixture was acidified with 5 N HCl. The polymer was filtered and washed with 10 mL of THF–diethyl ether (1:1), 10 mL of THF–ethanol (1:1), and 10 mL of THF. The organic layer of the combined acidic filtrate was concentrated to 5 mL by rotary evaporation and diluted with diethyl ether. Freshly prepared diazomethane solution[24] (6 molar equiv in diethyl ether) was added at −10 °C under nitrogen, and the solution was kept for 4 h at room temperature. *o*-Dichlorobenzene was added, and the concentration of methyl 3-phenylpropanoate was determined by GC analysis. Data are given in Tables I and II.

Acylation and Alkylation of Polymer-Bound Ester. (A) Small Scale. A single procedure was followed for gel and macroporous polymers with all degrees of cross-linking and functionalization. A 20% cross-linked macroporous polymer (3.0 g, 0.55 mmol of ester/g) was swollen in 15 mL of THF for 6 h. (The volume of THF used was the amount needed to swell the polymer plus a 5-mL excess.) A solution of 1.5 molar equiv of triphenylmethyllithium (0.38 M in THF)[25] was added by syringe through a rubber septum at room temperature under nitrogen. After 1 min the red color of base had faded, and 2.0 molar equiv of *p*-nitrobenzoyl chloride (Aldrich) in 5 mL of THF was added. The mixture was stirred mechanically for 3 h at room temperature. The polymer was filtered, washed with 10 mL of THF–diethyl ether (3:1), 10 mL of THF–ethanol (3:1), and 10 mL of THF, and dried at 30 °C under vacuum. A mixture of the dried polymer (3.0 g), 15 mL of THF, 1 mL of 50% aqueous KOH, and 0.05 g of tetra-*n*-butylammonium hydroxide (40% aqueous) was refluxed at 75 °C for 24 h. After cooling to room temperature, the mixture was acidified with 5 N HCl. The polymer was filtered and washed with 10 mL of THF and 10 mL of ethanol. The combined acid filtrate and 1 mL of concentrated HCl were refluxed for 1 h. The mixture was concentrated to an oil by rotary evaporation and diluted with diethyl ether. This solution was treated with diazomethane as in analysis of polymer-bound ester, and yields of 1-(*p*-nitrophenyl)-3-phenyl-1-propanone, 1,5-diphenyl-3-pentanone, and methyl 3-phenylpropanoate were determined by GC on column B at 270 °C. Trapping of the ester enolate with acetyl chloride, benzyl bromide, and 1-bromobutane was carried out by the same procedure used with *p*-nitrobenzoyl chloride in GC yield experiments.

The same procedure was followed with 1.5 molar equiv of lithium diisopropylamide (LDA)[20] as the base except that no color change could be observed as base was consumed. The LDA concentration in THF/hexane was 0.27 M when the polymer contained 0.18 mequiv of ester/g and 0.92 M when the polymer contained 1.08 mequiv of ester/g. One minute was allowed between additions of base and *p*-nitrobenzoyl chloride unless noted in Table IV.

(B) Large Scale. (1) *p*-Nitrobenzoyl Chloride Acylation. A mixture of 50.33 g (54.4 mmol) of 20% cross-linked macroporous polymer (1.08 mmol of ester/g) and 80 mL of THF was stirred mechanically for 30 min to swell the polymer. A solution of 81.5 mmol of 0.38 M triphenylmethyllithium in THF was added by syringe at room temperature under nitrogen. After 1 min, 20.1 g (0.11 mol) of *p*-nitrobenzoyl chloride in 20 mL of THF was added, and the mixture was stirred for 3 h at room temperature. The polymer was filtered with a fritted Buchner funnel, washed with 100 mL of THF–diethyl ether (3:1), 100 mL of THF–ethanol (3:1), and 100 mL of THF, and dried at 30 °C under vacuum overnight. A mixture of the dried polymer with 80 mL of THF, 10 mL of 50% aqueous KOH, and 0.5 mL of tetra-*n*-butylammonium hydroxide (40% aqueous) was refluxed at 75 °C for 1 day. After cooling to room temperature, the mixture was acidified with 5 N HCl. The polymer was filtered and washed with 100 mL of THF and 100 mL of ethanol. The acidic filtrate was combined with 5 mL of concentrated HCl, refluxed for 1 h, and cooled to room temperature. The solution was rotary evaporated to an oil, which was chromatographed through a column of 20 g of silica gel (Sargent-Welch, 28–200 mesh) with CCl_4–C_6H_6 (9:1). The solvent was evaporated, and the residue was crystallized from ethanol to give 5.58 g (40%) of 1-(4-nitrophenyl)-3-phenyl-1-propanone from ethanol as colorless plates, mp 73–75 °C (lit.[19] mp 74–75 °C).

The same procedure was used with 10% cross-linked gel polymer except that more THF was needed to swell and slurry the polymer. In all large-scale experiments slightly more THF is used than is needed to fill the space between the polymer beads. This is the smallest amount of solvent that still allows efficient mixing with a mechanical stirrer.

(2) Acetyl Chloride Acylation. A mixture of 25.62 g of polymer-bound ester (10% DVB gel, 0.67 mmol of ester/g) and 150 mL of THF was stirred for 30 min. A THF solution of 25.8 mmol of 0.38 M triphenylmethyllithium and 2.44 mL (34.3 mmol) of acetyl chloride were added at room temperature, and hydrolysis and decarboxylation were carried out as in the preceeding experiments. After the solvents were evaporated, 4-phenyl-2-butanone was purified by distillation at 50–60 °C (5 torr) [lit.[26] bp

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233-234 °C (760 torr)]. Its ^{1}H NMR and IR spectra were identical with those of an authentic sample (Aldrich, benzylacetone).

(3) 1-Bromobutane Alkylation. A mixture of 80 mL of THF and 49.82 g of polymer-bound ester (10% DVB gel, 0.67 mmol of ester/g) was treated with 43.5 mmol of triphenylmethyllithium and 4.75 mL (44.2 mmol) of 1-bromobutane (Aldrich) as in the preceeding experiments. The polymer was filtered and washed twice with 10 mL of THF and with 100 mL of ethanol. The solution was acidified with concentrated HCl, rotary evaporated to an oil, and diluted with diethyl ether. Freshly prepared diazomethane (6 molar equiv in diethyl ether) was added at -10 °C under nitrogen, and the solution was allowed to stand for 3 h at room temperature. After evaporation of the solvent, methyl 2-benzylhexanoate was obtained by column chromatography over silica gel with diethyl ether as the eluant. Evaporation of the ether gave 5.87 g of material whose ^{1}H NMR and IR spectra were the same as those of the independently synthesized compound.

(4) Benzyl Bromide Alkylation. The same procedure as above was followed with 75 mL of THF, 45.73 g of polymer-bound ester (10% DVB gel, 0.67 mmol of ester/g), 40.5 mmol of triphenylmethyllithium, and 4.9 mL (41.0 mmol) of benzyl bromide. After diazomethane methylation, methyl 2-benzylhexanoate was obtained by column chromatography over silica gel with diethyl ether as the eluant. Evaporation of solvent gave 5.92 g of material whose ^{1}H NMR and IR spectra were the same as those of the independently synthesized compound.

Recycling of Polymer. The first cycle used 40.0 g of 10% cross-linked gel polymer (0.67 mmol of ester/g) for *p*-nitrobenzoylation. The yield reported in Table VIII was isolated by the large-scale procedure. The recovered polymer was filtered, washed with 100 mL of THF-water (3:1), 10 mL of THF-ethanol (3:1), and 100 mL of THF, and dried at 30 °C under vacuum overnight. The dried polymer (36.67 g) in 150 mL of THF was swollen for 6 h, and 23.1 mmol of 0.38 M triphenylmethyllithium in THF was added at -40 °C under nitrogen with mechanical stirring. The mixture warmed slowly to room temperature. After it was cooled again to -40 °C, 3-phenylpropanoyl chloride (18.43 g, 108.5 mmol) in 10 mL of THF was added with mechanical stirring. The mixture warmed to room temperature and was stirred for 24 h. The polymer was filtered, washed with 100 mL of THF-diethyl ether (3:1), 100 mL of THF-ethanol (3:1), and 100 mL of THF and dried at 30 °C under vacuum overnight.

The second and third cycles of enolate *p*-nitrobenzoylation used the same procedures. The yield in Table VIII from cycle two was isolated. The yield from cycle three was determined by GC.

Acylation of Benzyl 3-Phenylpropanoate at Room Temperature. To a solution of 0.386 g (1.65 mmol) of benzyl 3-phenylpropanoate in 15 mL of THF in a 100-mL flask was added 2.475 mmol of triphenylmethyllithium in 3 mL of THF at room temperature with mechanical stirring. After 1 min, 0.61 g (3.3 mmol) of *p*-nitrobenzoyl chloride in 5 mL of THF was added. After 4 h, 1.6 g of 50% aqueous KOH was added, and the mixture was refluxed at 75 °C for 25 h. The mixture was cooled to room temperature and acidified with concentrated HCl. The solvents were evaporated, and the yields were determined by GC as described earlier (see Results).

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Registry No. 6a, 54914-77-1; **8**, 5396-91-8; **9**, 103-25-3; diethenylbenzene-(chloromethyl)ethenylbenzene copolymer, 9036-15-1.

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Applications of the Vilsmeier Reaction. 13. Vilsmeier Approach to Polycyclic Aromatic Hydrocarbons

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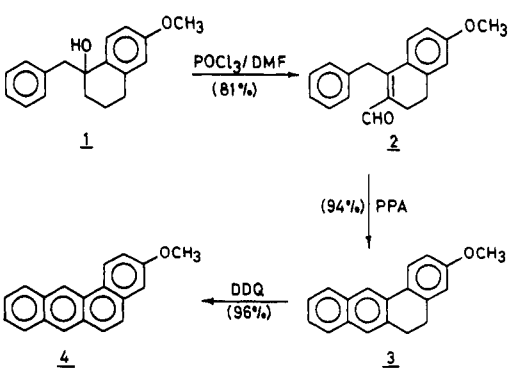
The synthesis of three typical polycyclic hydrocarbons (PAH) has been described, wherein the Vilsmeier reaction plays a major role. Vilsmeier reaction of the tetralol **1** gives the dihydronaphthaldehyde **2** which on cyclodehydration gives the dihydroarene **3**. Its dehydrogenation affords 3-methoxybenz[*a*]anthracene (**4**). Vilsmeier reaction on the dimethoxydihydronaphthalene **5** gives the versatile dimethoxydihydronaphthaldehyde **6** which has been converted to the dimethoxybenzo[*c*]fluorene **7** by direct cyclodehydration and the fulvene **10** by cyclodehydration of allylic alcohol **8** derived from **6** followed by dehydrogenation. The saturated alcohol **12** corresponding to **8** undergoes cyclodehydration to give the dimethoxyhexahydrobenzo[*c*]phenanthrene (**13**). Some of the advantages of the Vilsmeier approach to PAH have been pointed out.

Previous papers in this series deal with the application of the Vilsmeier reaction in the synthesis of diverse natural products (terpenoids,[1] chromenes,[2] and lignans[3]) and intermediates needed in the synthesis of bioactive molecules.[4] In this paper we present the synthesis of three typical polycyclic aromatics, benz[*a*]anthracene (**4**), two benzo[*c*]fluorenes (**7** and **10**), and a hexahydrobenzo[*c*]phenanthrene (**13**), wherein Vilsmeier reaction plays a key role. Because of the widespread environmental contamination of polycyclic aromatics and the high degree of hazard they pose to humans,[5] there is an ever increasing

Scheme I



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