Tetrahedron Letters No. 22, pp 1875 - 1878, 1977. Pergamon Press. Printed in Great Britain.

THE USE OF INSOLUBLE POLYMER SUPPORTS AS MONOBLOCKING GROUPS OF SYMMETRICAL DIACID CHLORIDES

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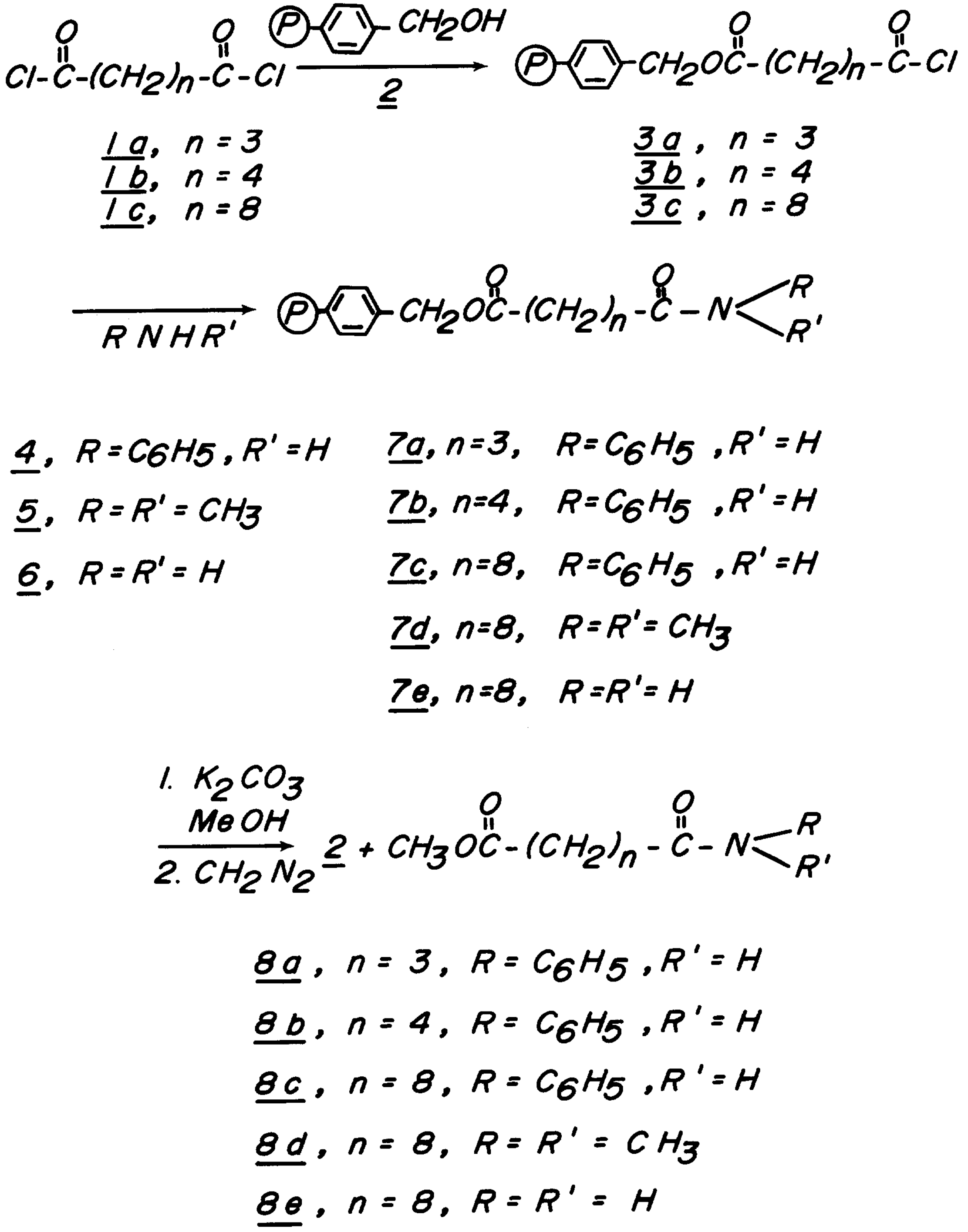
(Received in USA 2 March 1977; received in UK for publication 19 April 1977)

The difficulties encountered in effecting a chemical reaction at one end only of a completely symmetrical long chain diacid, diacid chloride, or diester is illustrated by the classical synthesis of monomethyl sebacate in which sebacic acid is treated with methanol and acid[1] or dimethyl sebacate is treated with base.[1,2] Both approaches yielded the desired monomethyl sebacate in under 45% yield, the remaining material being dimethyl sebacate and sebacic acid. We had previously shown how insoluble polymer supports can be used as monoblocking groups of symmetrical diols[3,4] and symmetrical dials[5,6] and have applied this procedure to the syntheses of insect sex attractants[7] and unsymmetrical carotenoids.[8]

For some time now we have been attempting to attach at one end only symmetrical diacids via their mono salts to a chloromethylated 2% crosslinked divinylbenzene-styrene Merrifield co-polymer[9] under a wide variety of conditions in which the solvent, the temperature, the counter ion, and the symmetrical diacid was varied. In all cases, it appeared that the major portion of the diacid was doubly-bound to the polymer irrespective of how much excess diacid was used.[10] Significant intraresin interactions have been previously demonstrated[11] and discussed[12] and our attachment of symmetrical diacids by both ends to the polymer, even when the mono salt of the diacid is present in large excess, represents another example of significant intraresin interactions.

The monoprotection of completely symmetrical diacids by insoluble polymer supports has now been achieved through their symmetrical diacid chlorides. In a typical procedure, 13 mmol of a diacid chloride (<u>1a-c</u>) was added to 3 g (3.48 meq) of an hydroxymethyl 2% crosslinked divinylbenzene-styrene copolymer (<u>2</u>)[13] suspended in 50 ml of dry tetrahydrofuran (THF) in a modified Schlenk tube apparatus[4] and stirred under argon for 12 h at room temperature. The polymer-bound monoblocked acid chlorides (<u>3a-c</u>) were filtered under argon and washed with dry THF. Polymers <u>3a-c</u> were treated with aniline (<u>4</u>) and <u>3c</u> with dimethylamine (<u>5</u>) and ammonia (<u>6</u>) in dry THF to give the polymer-bound monoester monoamides (<u>7a-e</u>) which on hydrolysis with tetrabutylammonium hydroxide in THF or potassium carbonate in methanol


2
1a, n = 3
1b, n = 4
1c, n = 8
3a, n = 3
3b, n = 4
3c, n = 8
RNHR'
4, R = C6H5, R' = H
5, R = R' = CH3
6, R = R' = H
7a, n=3, R=C6H5, R'=H
7b, n=4, R=C6H5, R'=H
7c, n=8, R=C6H5, R'=H
7d, n=8, R=R'=CH3
7e, n=8, R=R'=H
1. K2CO3 MeOH
2. CH2N2
2
8a, n = 3, R = C6H5, R' = H
8b, n = 4, R = C6H5, R' = H
8c, n = 8, R = C6H5, R' = H
8d, n = 8, R = R' = CH3
8e, n = 8, R = R' = H

yielded crude monoacid monoamides which were not isolated but immediately converted to the monoester monoamides with diazomethane. Although the products obtained were reasonably pure, they were further purified on preparative thin-layer chromatography (eluant ether-benzene, 3:7) to see if any symmetrical dimethyl esters could be isolated. In control experiments, 4% of the symmetrical dimethyl esters could be detected in this system, in the presence of 96% monoester monoamides. The only products isolated were the monomethyl ester monoamides (8a-e). Compounds 8a-e were obtained in high yield (Table I) and no diesters resulting from unreacted 3a-c or diacid chloride doubly-bound to the polymer were detected.

Table I. Reaction of Polymer-bound Acid Chlorides with Amines

Acid Chloride	Amine	Monoester Monoamide[a]	Quantity of 1a-c/g of 2	Quantity of 8a-e/g of 2	Yield	mp
			mg/g (mmol/g)		%	°C
$ClOC(CH_2)_3COCl$ (1a)	4	$CH_3O_2C(CH_2)_3CONHC_6H_5$[b]	67 (0.42)	86 (0.39)	93	68
$ClOC(CH_2)_4COCl$ (1b)	4	$CH_3O_2C(CH_2)_4CONHC_6H_5$[b]	50 (0.32)	73 (0.30)	94	43
$ClOC(CH_2)_8COCl$ (1c)	4	$CH_3O_2C(CH_2)_8CONHC_6H_5$[c]	113 (0.56)	161 (0.55)	98	66[d]
1c	5	$CH_3O_2C(CH_2)_8CON(CH_3)_2$[c]	113 (0.56)	117 (0.48)	86	oil
1c	6	$CH_3O_2C(CH_2)_8CONH_2$[c]	113 (0.56)	108 (0.50)	90	73[e]

[a] All new products gave satisfactory elemental analyses and exhibited spectral properties in accordance with the assigned structures.

[b] Obtained by cleavage with tetrabutylammonium hydroxide

[c] Obtained by cleavage with potassium carbonate in methanol.

[d] Literature mp 68°.[1]

[e] Literature mp 74-76.[2]

The initial loading capacities of 2 for 1a and 1b were determined by treatment of 3a and 3b with aqueous dioxane, followed by base cleavage and treatment with diazomethane which gave dimethyl glutarate and dimethyl adipate respectively. The capacity of 2 for 1c was determined as above but omitting the treatment with diazomethane and the sebacic acid was recovered by simple ether extraction.

The synthesis of monoester monoamides 8a-e by the use of insoluble polymer supports represents a substantial improvement over classical[1,2] and modern[14] syntheses of this type. It has also been demonstrated that variations in conditions and in reaction schemes can alter the ability of a polymer to undergo intraresin reactions.

Acknowledgement. This research was supported by a grant from the National Research Council of Canada.

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