

Organic Synthesis Of Polymers By Polymeric Solid Phase Reagents

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Abstract : Medicinal chemists in the pharmaceutical business currently routinely use solid-phase organic synthesis (SPOS) to plan libraries of little organic molecules for screening. The present enthusiasm for solid-phase organic synthesis has prompted a restored enthusiasm for an integral method where solid-bolstered reagents are utilized in arrangement phase science. This system deters the requirement for connection of the substrate to a solid-support and empowers the scientific expert to screen the responses utilizing well-known investigative methods. The qualities and along these lines capacity of a polymer can be custom fitted by adjusting its length and the substituents showed on the spine.

Keywords: Polypeptides, Polyethylene glycol, SPOS,

1 INTRODUCTION

Solid-phase synthesis is a technique whereby manufactured changes are directed with one of the reactant molecules appended to an insoluble material alluded to as the solid help. It was initially created for peptide synthesis. Since the ongoing effect of combinatorial science, solid-phase strategies have been applied all the more for the most part to organic synthesis. One of the prerequisites of solid-phase science is a linker to join a substrate molecule to the solid phase. As synthesis continues, this material is changed into the item, which can be at long last expelled by cleavage of the linker. The synthesis of peptides doesn't happen on the outside of a genuinely solid material, however rather inside gel-like network of associated polymeric molecules swollen by dissolvable molecules. Indeed, the peptide was integrated on a profoundly liquid and arrangement like condition. The improvement of this procedure of solid-phase organic synthesis (SPOS) was at first prodded by the encouraged item purging; the response items stayed bound to an insoluble pitch and reagent abundances were essentially expelled by continued flushing. An insoluble pitch, frequently cross connected polystyrene (PS) was functionalized with a linker moiety conveying an utilitarian gathering to which the substrate was associated. A response or grouping of responses was conveyed put to change over the upheld substrate I into the bolstered item and overabundance reagents were washed away after each progression. At long last, particular cleavage yielded unadulterated item in arrangement and the insoluble help, which was reused for further use. The first technique for Merrifield's dipeptide synthesis on a polymer support has since been stretched out fundamentally to each sort of response in organic science, including polypeptide, polysaccharide, and polynucleotide synthesis.

Since bolstered synthesis is entirely manageable to computerization, it has become a significant manufactured strategy. The potential abuse of polymer bolstered species in concoction process has pulled in impressive mechanical intrigue and as of late, commercialization of various frameworks has been accomplished and these species are viewed as 'high worth polymers'. Various legitimate reading material covering the point by point study of this territory has just been distributed. Immobilization of a receptive animal types on a help give various significant points of interest like 'naturally visible handle for partition and cleansing, maintenance of valuable species, 'exemplification' of destructive, harmful or dangerous species, adjustment of responsive species completing compound synthesis which diminishes side responses and upgrades selectivity with extensive reactivity. The gigantic increment in the quantity of papers depicting the utilization of polymeric backings in organic synthesis over the previous decade is a clear show of its effect in the concoction network. The points of interest picked up by this procedure are hitting with four principle factors. The simplicity of science is the fundamental factor - responses can be completed in three stages: expansion of reagents, sifting and washing of the sap. Second factor is end of cleansing in each progression. For each progression of a multi-step synthesis, the main purging required is a tar washing step. Just the last result of cleavage should be cleansed. The third angle is that, in a solid phase synthesis, high convergence of the reagents can be utilized to drive the response to finishing. Solid phase synthesis of little organic molecules has gotten recharged consideration since the primary report of the polymer upheld synthesis of mixes of restorative intrigue. Solid phase synthesis is presently a key segment of the high-throughput synthesis and screening way to deal with medicate revelation, the procedure of using insoluble polymeric backings for completing organic compound change has accomplished wide spread acknowledgment as prove by the presence of an enormous number of research papers, audits, monographs and books.

Polymer supports: general considerations

Regular tars utilized in SPOS are gotten from softly cross-connected polystyrene, polyethylene glycol (PEG)- joined polystyrene and full-scale permeable polystyrene. Polystyrene tars are all the more generally utilized as they have more noteworthy compound dependability. Tile

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overpowering inclination for dabs as a help group has to a great extent restricted tar contender to those dependent on styrene and acrylates, in view of the necessities for suspension polymerization. A significant option in contrast to globules is naturally visible items, for instance, sticks, in light of joined polyolefin, which has discovered far-reaching use in combinatorial parallel synthesis. Every one of these help types will be portrayed beneath. A significant part of SPOS is the dissemination of reagents to the responsive locales on bound molecules. For gently cross-connected polystyrene and PEG join saps it is commonly necessitated that the globules swell in the response dissolvable, setting up a phase that is around 10-20% polymer and 80-90% dissolvable. The versatility of polymer-bound molecules and reactants inside the swollen gel is legitimately identified with the degree of growth. Large scale permeable polystyrenes are profoundly cross-connected permeable saps and permit reagent dispersion through a pore organize inside the globules, as opposed to through spaces between dabs in a swollen polymer gel. The benefits of SPOS comparative with arrangement phase synthesis are a sign of three qualities related to the procedure (Table 1): simplicity of filtration, specific item cleavage and confinement of response destinations. The most convincing bit of leeway of solid-phase synthesis is the simplicity of decontamination, wherein reactants and results not consolidated in the gum bound molecule are promptly evacuated by redundant dissolvable washing. The effortlessness of item purging and separation permits computerization of multistep synthesis utilizing instrumentation dependent on liquid conveyance and filtration. Since bound polluting influences are not promptly distinguishable, solid-phase synthesis requests the utilization of powerful, high return responses to accomplish the last results of high immaculateness after cleavage from the help. In the previous, not many years, the universe of organic responses that have been effectively adjusted to solid-phase has expanded significantly, demonstrating that appropriate determination of sap and response conditions can give manufactured systems that have the essential loyalty for use in solid-phase synthesis [12^o]. Besides, the virtue of the cut item can regularly be improved by structuring a cleavage particular towards the ideal item. This frequently includes cyclization to impact the cleavage technique and has been applied to the synthesis of diketopiperazines [13^o] and cyclic ethers [14^o]. Solid-phase responses are for the most part more slow than arrangement phase partners; nonetheless, quick responses are regularly watched, as on account of lied development from gum bound 3-amino phosphonium salts, where response times of 5 min at 0°C were ideal.

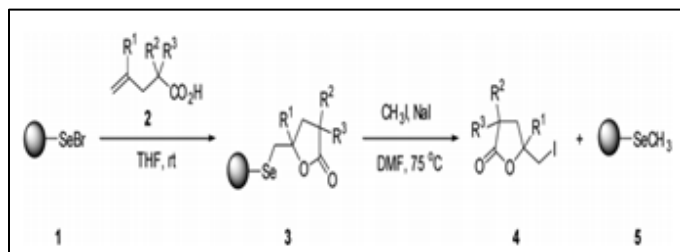
Table 1 Solid phase organic synthesis advantages

Characteristic	Advantages
The desired product remains bound to the polymer phase throughout the synthetic sequence, whereas reactants and by-products remain in solution	Products are purified by filtration and washing. Reactions can often be driven to completion through the use of excess solution phase reagent. Multistep syntheses are amenable to automation. Selective liberation of high purity product.
Production cleavage can be selective towards the structural and functional elements of the desired molecule. The polymer can restrict the	Site isolation

Confinement of the association of polymer-bound response destinations is an alluring element of polymer upheld responses. The capacity to accomplish site detachment is subject to various factors and is very case-explicit. The utilization of pitches with low practical gathering stacking and higher cross-connecting levels for the most part builds site separation. Another advancement in polymeric backings is the radio-recurrence (RF)- labeled microreactors, where the one of a kind location related with the tile tag is followed remotely by a peruser. Gatherings of microreactors can be arranged and assembled at each progression of an engineered succession, permitting the synthesis of a variety of discrete mixes utilizing regular china. RF labeling has been applied to both globule compartments and polystyrene-united polypropylene tubes alluded to as MicroKans and Micro-Tubes individually. The Micro-Tubes were as of late applied to the planning of a tryphostin library. A practically equivalent to labeling framework, alluded to as Tran-Stems, has showed up for Syn-Phase crowns where the RF tag is available in the stein.

2 METHODS

Solid-phase organic synthesis (SPOS) utilizing insoluble solid backings, for example, polystyrene resins shows various points of interest when contrasted with arrangement science. The most striking one is the plausibility of applying abundances of reagents and expelling them without including tedious partition systems. Mixes bearing the subbed \square -butyrolactone moiety are across the board in nature and have gotten a lot of intrigue as a result of their physiological properties. In addition, functionalized \square -butyrolactones have significant organic properties and are otherwise called beginning material for the planning of pharmacologically dynamic mixes. In this way, numerous techniques have been produced for the synthesis of \square -butyrolactone ring frameworks. Among these strategies, seen advanced cyclization responses of olefinic carboxylic acids are valuable techniques for the development of functionalized \square -butyrolactones. Be that as it may, organoselenium reagents consistently have a foul smell and are very dangerous, which is frequently risky in organic synthesis. Since the first organo-selenium resin utilized in SPOS with a joined favorable position of diminishing unpredictability and improvement of item workup was accounted for in 1976, a few research bunches have created selenium-based methodologies for SPOS. As of late, our examination bunch has been keen on the use of organic selenium resins for the synthesis of some useful heterocyclic mixes, for example, 5-iodoisoxazolines, 2-monomethyl-2,3-dihydro benzofurans, and vinyl-subbed 1,3,4-oxadiazoles. As a component of a continuous program concentrated on the utilization of polymeric organoselenium reagents in SPOS, we here portray a straightforward and proficient manufactured way to deal with 5-monomethyl-dihydrofuran-2-ones (Scheme 1). As far as anyone is concerned, there was no report concerning the planning of 5-iodomethyl-dihydrofuran-2-ones utilizing this innovation.



Scheme 1. Solid-phase synthetic route to 5-iodomethyl-dihydrofuran-2-ones

Clearly, polymer-bolstered selenolactonization would be the key advance for the accomplishment of this convention. Strangely, just mixing the resin 1 in tetrahydrofuran (THF) at room temperature with 3.0 equiv of the α,β -unsaturated acids (2) brought about a quick decolorization of the resin. Subsequent to blending for 2 h, the ring-conclusion response on the solid phase was finished, which was dictated by the natural investigation of 5-selenomethyl-dihydrofuran-2-ones (3) (Br was imperceptible). Furthermore, the response was likewise checked by Fourier change infrared (FT-IR) of resin (3), demonstrating a solitary solid top around 1770 cm^{-1} , which showed that the lactonization was finished. Moreover, expanding the measure of α,β -unsaturated acids to 4 or 5 equiv, supplanting THF with different solvents, for example, CH_2Cl_2 and CH_3CN , or delaying the response time had little impact on the cyclization. Dissolving focuses were uncorrected. ^1H NMR (400-MHz) and ^{13}C NMR (100-MHz) spectra were recorded on a Bruker Avance (400-MHz) spectrometer, utilizing CDCl_3 as the dissolvable and TMS as the inside standard. FT-IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. Microanalyses were performed with a Carlo Erba 1106 natural analyzer. Polystyrene for the readiness of polystyrene-upheld selenium bromide as per the system portrayed by Nicolaou was obtained from Aldrich (100–200 work, cross-connected with 1% divinylbenzene). 4-Pentanoic corrosive (2a) is industrially accessible, and the other α,β -unsaturated acids, for example, 2-methylpent-4-enoic corrosive (2b), 2-ethylpent-4-enoic corrosive (2c), 2-allyl-3-benzenepropanoic corrosive (2d), 2,2-dimethylpent-4-enoic corrosive (2e), 2,2-diphenylpent-4-enoic corrosive (2f), 4-methyl-4-pentanoic corrosive (2g), and 4-phenyl-4-pentanoic corrosive (2h) were set up as per the revealed technique. DMF was refined from calcium hydride, and THF was refined from sodium benzophenone quickly preceding use. Different reagents were acquired from business providers and utilized moving along without any more sanitization.

3 RESULT

Under a progressive weight of nitrogen, α,β -unsaturated acid 2 (3 mmol) was added to polystyrene-reinforced selenium bromide 1 (1.0 g, 1.18 mmol $\text{Br}=\text{g}$) swollen in THF (15 mL) for 30 min. The suspension was blended at room temperature for 2 h. The blend was sifted, and the resin was washed with THF (10 mL 3) and CH_2Cl_2 (10 mL X 3) and dried under vacuum to bear the cost of dry 5-selenomethyl-dihydrofuran-2-one resin 3. NaI (1.5 g) and CH_3I (1.5 mL) were added to a suspension of the swollen resin 3 (1.0 g) in dry DMF (15 mL) under nitrogen. The

suspension was mixed at 75 C for 20 h. The blend was separated, and the lingering resin 5 was washed with CH_2Cl_2 (10 mL 3). The filtrate was washed with immersed $\text{Na}_2\text{S}_2\text{O}_3$ and H_2O , separated with ethyl acetic acid derivation (10 mL 3), dried over anhydrous Na_2SO_4 , and vanished to outfit unrefined items 4a–4h with 93–98% virtue as controlled by superior fluid chromatography (HPLC), which were additionally purged by section chromatography ($\text{EtOAc}=\text{hexane}$, 20=1–12=1, v=v) over silica gel to give unadulterated 5-iodomethyl-dihydrofuran-2-ones (4a–4h) for their ^1H NMR, ^{13}C NMR, and essential examinations.

Table 1 4a-4h 5-iodomethyl-dihydrofuran-2-ones

Entry	R ¹	R ²	R ³	Product	Yield (%) ^a
1	H	H	H	4a	96
2	H	H	H	4a ^b	94
3	H	H	H	4a ^c	92
4	H	H	Me	4b	94 (dr 6:1)
5	H	H	Et	4c	95 (dr 6:1)
6	H	H	$\text{C}_6\text{H}_5\text{CH}_2$	4d	93 (dr 5:1)
7	H	Me	Me	4e	90
8	H	C_6H_5	C_6H_5	4f	90
9	Me	H	H	4g	94
10	C_6H_5	H	H	4h	92

^aOverall yields based on polymer-supported selenium bromide 1 (1.18 mmol $\text{Br}=\text{g}$).
^bWith the third regenerated resin 1.
^cWith the fourth regenerated resin 1.

As seen from Table 1, the only 5-exo-trig ring-closing reaction induced by selenium bromide resin was preferred because the other possible regioisomer from a 6-endo-trig closure was not observed. For the α -substituted acids (2b, 2c, and 2d), a mixture of two diastereoisomers was obtained, and NMR studies showed that synlactones were the major isomers (Table 1, entries 4–6). For α,β -disubstituted substrates (2e and 2f), the cyclization also proceeded well, although with a little bit lower yields of target compounds (4e and 4f). Also, it ought to be noticed that the polystyrene-upheld selenium bromide (1) is effectively recovered structure the recuperated methyl selenide resin (5) (Scheme 2) and can be reused for the change of α,β -unsaturated acids to 5-iodomethyl-dihydrofuran-2-ones (4). For instance, after the fourth recovery and use, the yield of 5-iodomethyl-dihydrofuran-2-one (4a) was practically same as when crisply arranged selenium bromide resin was utilized.

5 CONCLUSION

The ongoing increase in SPOS has powered a recharged enthusiasm for polymeric backings. Gently cross-connected polystyrene resins proceed as the workhorse materials; in any case, the craving to enhance their lacks has prompted the advancement of new supports. The more extensive dissolvable similarity of these backings is the hugest improvement and frequently permits the exchange of dissolvable frameworks straightforwardly from known arrangement phase science; and a more extensive range, m of wash solvents for side-effect evacuation. RF-labeled micro reactors can be applied to coordinate arranging procedures, which give an effective way to delivering libraries of discrete mixes.

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