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Multipin Solid Phase Synthesis of Ethers Using Modified Mitsunobu Chemistry

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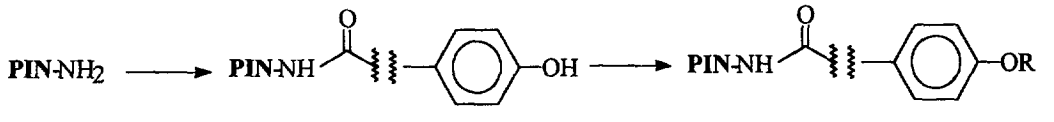
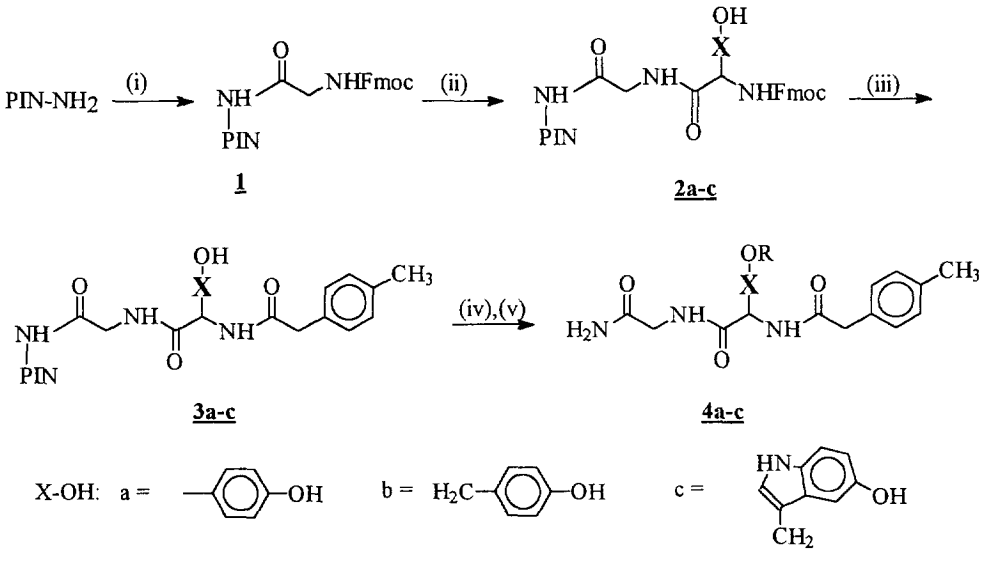
Abstract: *Formation of ether derivatives of phenolic containing structures using solid phase Mitsunobu chemistry on functionalized polyethylene pins was investigated. Using the Multipin approach, a range of reaction parameters were systematically varied in parallel experiments including solvent, temperature, time, reactant concentrations, base, phosphine and alcohol to determine optimum reaction conditions. Solid phase reaction of three phenols with a range of alcohols to form the ethers was found to proceed smoothly using 0.15M PPh_3/DEAD/alcohol in THF at 37 °C for 4 days in the presence of 0.45M triethylamine.* Copyright © 1996 Published by Elsevier Science Ltd

The use of solid phase synthesis for the generation of diverse libraries of non-peptide compounds for drug discovery is an area that has expanded rapidly in recent times.[1,2] Solid phase synthesis of non-peptide molecules including peptoids,[3] benzodiazepines,[4] β-turn mimetics,[5] hydantoins [6] and ureas [7] has recently been reported. In addition, a number of useful solid phase reactions have been reported including the Heck reaction,[8] Suzuki cross coupling,[9] Michael addition[10] and Horner-Emmons condensation[10] reactions. The majority of solid phase synthesis to date has been carried out on polystyrene resin as popularized by Merrifield.[11] However, solid phase synthesis of benzodiazepines[12] and β-turn mimetics[5] on grafted polyethylene pins using the Multipin approach[13] has also been reported. Synthesis of the β-turn mimetics on polyethylene pins on average gave products that were of higher purity than the equivalent compounds synthesized on a PEG-polystyrene based resin.[5] Our recent reports of the solid phase synthesis of oligomers of acyl-2,3-diaminopropionic acid[14] and the reductive amination of a pin-bound ketone[15] further illustrate the utility of the Multipin approach for solid phase organic synthesis. We report here the application of modified Mitsunobu chemistry to Multipin solid phase synthesis of ethers as shown in Scheme 1.



Scheme 1: Alkylation of pin-bound phenols.
PIN = [Polyethylene Pin]-[MA/DMA]-HMD-$COCH_2NH$-(Rink handle)[16]

We were interested in preparing libraries of compounds based on a series of trifunctional phenolic templates. Generation of large numbers of variants of such molecules could be achieved by conversion of the phenolic hydroxyl to a range of ethers by reaction with a readily available and diverse class of reagents such as alcohols. Although, phenols can react with alkyl and aryl halides to form ethers,[17] we chose to focus on ether formation using Mitsunobu chemistry [18-20] which is mild and utilizes alcohols as the source of the alkyl or aryl substituent (R). To investigate the Mitsunobu reaction on the solid phase, three model phenolic structures **3a-c** were assembled using the Multipin approach (Scheme 2) and initially, structure **3a** (which contains D-4-hydroxyphenylglycine) was used as the model system to investigate a range of variables.



Scheme 2: Assembly and alkylation of Model Phenols **3a-c**. (i). Fmoc-Gly-OH / BOP / HOBt / NMM / DMF, 2 h. (ii). 20% piperidine / DMF, 30 min, then Fmoc-NH-CH(X-OH)-CO_2H / DIC / HOBt / DMF, 20 h. (iii). 20% piperidine / DMF, 30 min, then p-Tolylacetic acid / DIC / HOBt / DMF, 20 h. (iv). 10% ethanolamine / DMF, 1 h then Pph_3 / DEAD / alcohol (R-OH) / solvent [21]. (v) 95%TFA / H_2O. PIN defined as per Figure 1.

In the initial experiments, a number of different variables were investigated simultaneously[15] in order to determine the optimum conditions for ether formation. These included solvent (THF, DMF, dioxan, DME, DMA, DCE) , temperature (20, 37 and 65°C), reaction time (1-4 days), reactant concentrations, phosphine (PPh_3, P(4-Cl-C_6H_4)$_3$, P(n-Bu)$_3$), presence of base and type of alcohol. From these experiments, the following results were obtained. 1) Triphenylphosphine gave the best results; P(4-Cl-C_6H_4)$_3$ gave no improvement over PPh_3 and P(n-Bu)$_3$ was ineffective. 2) The following reagent concentrations were found to be optimal: PPh_3 (0.15M) / DEAD (0.15M) / alcohol (0.15M) / TEA (0.45M). 3) Ether solvents were most effective with THF affording the highest conversions on average. 4) Addition of TEA improved conversion to the ether **4**. 5) Reactions at 37°C gave better conversions than those at room temperature. No improvement in conversion was obtained when the temperature was increased to 65°C. 6) Adequate conversion was obtained after 48 hours but was increased after 96 hours. 7) Ether formation with a variety of primary and secondary alcohols is possible.

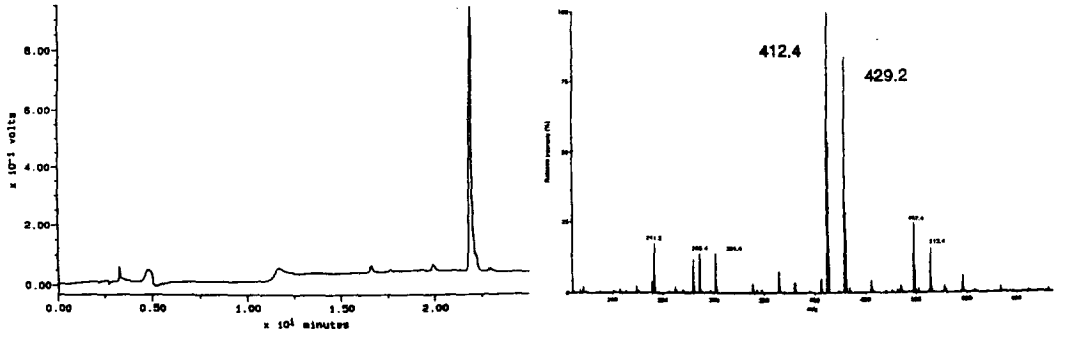
Table 1 lists some of the results obtained after treatment of model systems **3a-c** with a range of alcohols using the optimum conditions determined from these experiments (Pph_3 / alcohol / DEAD / TEA / THF / 37°C / 4 days, concentrations as given above). Figure 1 shows an HPLC and ionspray MS trace of a representative product (**4b**, R = n-Pr). The results indicate that reaction of the pin bound phenols with a range of primary alcohols including aliphatic, aromatic and heterocycle substituted alcohols afford the corresponding ethers with high conversion. The percentage conversions presented in Table 1 are based on HPLC peak areas at 214 nm; product identy was confirmed by ionspray MS. Generally, reactions gave the target ether as the major product with traces of the starting phenol and triphenylphosphine oxide as minor contaminants.

In summary, we have described a simple method for the generation of ethers in high purity on solid phase by the Multipin method. Utilization of the large variety of alcohols and phenols available should allow construction of diverse libraries of compounds based on these building blocks.

Table 1. Reaction of **3a-c** with a range of alcohols. Characterization data for ether products (**4**).

Support bound phenol	Alcohol	% Conversion to ether (4)[a]	Ion spray MS data: calcd/found[b] $[M+1]^+$
3a	n-butanol	95	412 / 412
3a	3-hydroxymethyl pyridine	99	447 / 447
3a	3-pyridinepropanol	99	474 / 474
3b	n-propanol	99	412 / 412
3b	2-ethoxyethanol	99	442 / 442
3c	isopropanol	94	451 / 451

a: HPLC recorded on a Waters HPLC system using a 5μm Merck Lichrosphere 100 RP-18 column (25 cm). Linear gradient A (0.1% TFA(aq) to B (0.1% TFA in water/MeCN (2:3)). b: MS recorded on a Perkin Elmer Sciex API III Biomolecular Mass Analyser.



(i) (ii)

Figure 1: HPLC (i) and ionspray MS (ii) of reaction product **4b** (R = n-Pr). Peak assignment: m/z 412.4, $[M+H]^+$; m/z 429.2, $[M+NH_4]^+$.

REFERENCES AND NOTES

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Abbreviations: BOP: Benzotriazole-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate; DCE: 1,2-dichloroethane, DCM : dichloromethane, DEAD: diethyl azodicarboxylate, DIC: diisopropylcarbodiimide, DMA: N,N-dimethylacetamide, DME: Dimethoxyethane, DMF: N,N-dimethylformamide, Fmoc: fluorenylmethoxycarbonyl, HMD: hexamethylenediamine, HOBt: 1-hydroxybenzotriazole, HPLC: high performance liquid chromatography, MA/DMA: methacrylic acid/dimethylacrylamide co-polymer, MS: mass spectrometry, NMM: N-methylmorpholine, $P(n\text{-}Bu)_3$: tri-n-butylphosphine, PEG: polyethyleneglycol, $P(4\text{-}Cl\text{-}C_6H_4)_3$: tris(4-chlorophenyl)phosphine, PPh3: triphenylphosphine, Rink handle: 4-[α-amino-2,4-dimethoxybenzyl]-phenoxyacetic acid, TEA: triethylamine, TFA: trifluoroacetic acid, THF: tetrahydrofuran.

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21. Ether formation: Pins with model systems **3a-c** linked via the acid labile Rink handle were thoroughly dried under vacuum and a solution of PPh_3/DEAD/alcohol/THF (0.15M in each reagent) containing TEA (0.45M) added (0.5 ml/pin). Reactions were carried out in sealed 2 ml centrifuge tubes at 37°C for 4 days after which the pins were removed, washed with DMF and DCM, and then the products cleaved by treatment with 95% TFA/5% water for 90 min. Solvent was removed under a stream of nitrogen and samples dissolved in 60% acetonitrile/water for reverse phase HPLC and ionspray MS analysis.

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