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Carbon–carbon bond formation via the Mitsunobu reaction on solid supports

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Abstract

The feasibility of C–C bond formation via the Mitsunobu reaction on solid supports has been investigated. Alkylation of a polymer supported alcohol with various compounds having an active methylene moiety in the presence of TMAD and Bu_3P gave the desired monoalkylated product, as well as an unexpected bis-alkylated product in ratios depending on the substrate loading. A rationalization for the latter is also presented. © 1999 Elsevier Science Ltd. All rights reserved.

In the past several years the potential of combinatorial chemistry to generate libraries of small molecules has been investigated extensively to expedite the overall drug discovery process. This has stimulated interest among chemists to perform the synthesis of organic molecules using solid-phase protocols in areas other than DNA and peptides. The application of the classical Mitsunobu reaction to generate alkyl ethers on solid-phase has been recently reported in the literature by several groups.[1–3] One of the most common chemical transformations in organic chemistry is the formation of the C–C bond. The use of the Mitsunobu reaction in directly generating a C–C bond obviates the need for prior activation of an alcohol. One such example involves the use of *o*-nitroarylacetonitriles as carbon acids in the Mitsunobu reaction.[4] Subsequently, Tsunoda et al. examined the utility of the Mitsunobu reaction in generating carbon–carbon bonds in the solution phase by directly reacting active methylene compounds for such reactions.[5] Recently, solid phase synthesis of *N*-alkyl sulfonamides was reported in the literature, however, the feasibility of the Mitsunobu reaction has not yet been explored for carbon–carbon bond formation on solid-phase.[6] The products from a solid-phase Mitsunobu alkylation reaction involving active methylene compounds such as α-ketonitrile, diethylmalonate, β-ketoacetate provide novel intermediates for generating molecular diversity. These intermediates are extremely useful and can be easily converted into heterocyclic compounds possessing biological activity such as pyrazoles, isoxazoles, indole, and tryptophan derivatives.[7–12] Given the prospects of the 1,3-dicarbonyl compounds in the drug discovery process, we became interested in developing this chemistry. Here, we report the scope and the limitation of the Mitsunobu reaction in generating C–C bonds in the solid-phase.

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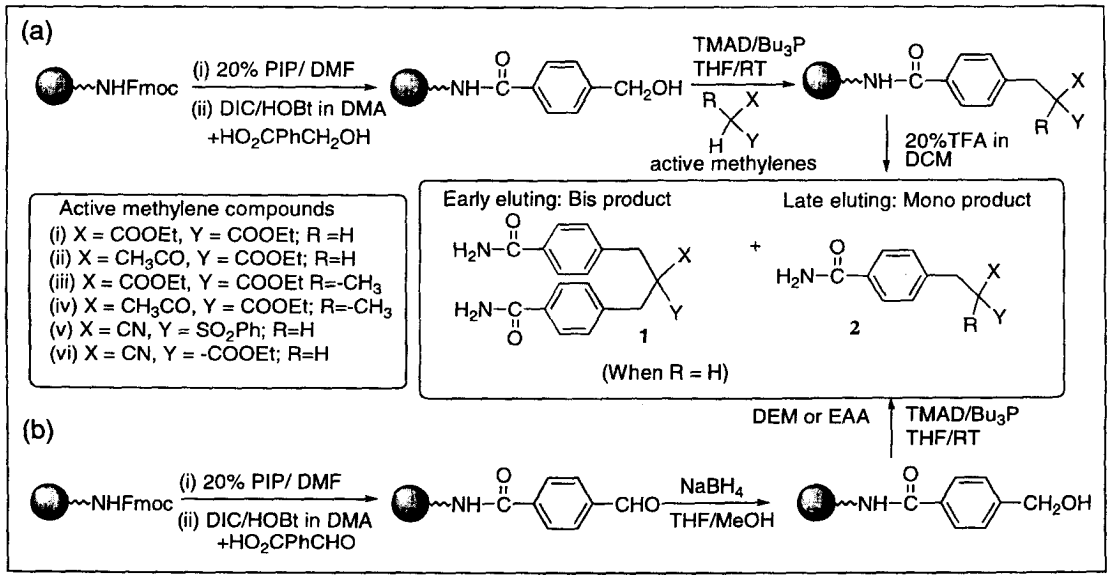
In our strategy, the title reactions require a unit containing the alcohol moiety to be attached to the polymer support.[13] For this, the Fmoc protecting group of the polystyrene-Rink linker support was removed by brief treatment (5–10 min) with 20% piperidine (PIP)† in DMF at rt to provide the pendant amino group. The amino group was then coupled with 4-(hydroxymethyl)benzoic acid (HMBA) using DIC and HOBt to provide the solid-phase supported alcohol for Mitsunobu alkylation (Scheme 1a). Typical C–C bond formation was accomplished by reacting the resin bound alcohol with a fivefold excess of *N,N,N′,N′*-tetramethylazodicarboxamide (TMAD), tributyl phosphine (Bu_3P) and the active methylene compounds such as diethylmalonate, ethylacetoacetate, cyanoethylacetate, (cyanomethyl) phenylsulfone, diethyl methylmalonate, and ethyl 2-methylacetoacetate in THF at rt over 12 h. Finally the products were released from the resin by treatment with 20% TFA in CH_2Cl_2.



Scheme 1.

The results from the HPLC, mass spectral, and NMR analysis of the cleaved products are given in Table 1. The HPLC chromatogram, shown in panel a of Fig. 1, clearly shows the formation of two products in ratio of 1:1.2. In order to probe the structures, in each case the separation and isolation of the pair of compounds were achieved by preparative TLC (SiO_2). The structures 1 and 2 were determined by mass and NMR spectral analysis. We were initially uncertain whether a dimeric ester (structure is shown in reference)[14a] was formed during the polymer loading. This product could undergo C–C bond formation (structure shown in reference).[14b] Such a product differs from the bis-alkylated product (Scheme 1) by 1 amu. Thus we undertook the alternative strategy as shown in Scheme 1b. This scheme precludes the diester formation. However, in this route we obtained the same ratio of bis- vs mono-alkylated products as in Scheme 1a. This conclusively showed that the bis-alkylation occured during the Mitsunobu coupling.

† Abbreviations: DIC: diisopropylcarbodiimide; HOBt: 1-hydroxybenzotriazole; PIP: piperidine; TFA: trifluoroacetic acid; Fmoc: 9-fluorenyl-methoxycarbonyl; TMAD: *N,N,N′,N′*-tetramethylazodicarboxamide; DMF: dimethylformamide; TEAA: triethylammonium acetate buffer; DEM: diethyl malonate; EAA: ethylacetoacetate; Bu_3P: tributyl phosphine; HMBA: 4-(hydroxymethyl)benzoic.

Table 1

Active methylene compounds	HPLC t_R (min)	(M+1)	% Purity	NMR data in obtained in $CDCl_3$ unless stated otherwise.
$CH_2(COOEt)_2$	12.1 12.3	294.3 427.2 *294.1331* *427.1842*	81[a]	**Mono:** 7.28 (d, 2H$_{Ar}$, *J*=8.1), 7.75 (d, 2H$_{Ar}$, *J*=8.1), 4.2 (m, -CH_2-), 3.65 (t,-CH_2-), 1.2 (t,-CH_3) **Bis:** DMSO-d_6 7.21 (d, 2H$_{Ar}$, *J*=7.8), 7.8 (d, 2H$_{Ar}$, *J*=7.9), 3.25 (br s, 4-CH_2-), 4.02 (q,-CH_2-), 1.15 (q,-CH_3)
$CH_3CH(COOEt)_2$	14.5	308.3	77[b]	7.26 (d, 2H$_{Ar}$, *J*=8.0), 7.76 (d, 2H$_{Ar}$, *J*=8.0), 4.2 (q, -CH_3), 3.32 (s,-CH_2-), 1.36 (s,-CH_3), 1.23 (t,-CH_3)
CH_3COCH_2COOEt	11.9 12.3	264.3 397.3	80[a]	**Mono:** 7.3 (d, 2H$_{Ar}$, *J*=8.0), 7.70 (d, 2H$_{Ar}$, *J*=8.0), 4.18 (q, -CH_2-), 3.85 (t,-CH-), 3.2 (m,-CH_3), 2.2 (s,-CH_3), 1.2 (t,-CH_3) **Bis:** 7.20 (d, 2H$_{Ar}$, *J*=7.9), 7.7 (d, 2H$_{Ar}$, *J*=7.8), 4.15 (q, -CH_2-), 3.22 (q,-CH_2-), 2.01 (s,-CH_3), 1.9 (t, -CH_3)
$CH_3COCH(Me)COOEt$	14.7	277.3	75[b]	7.21 (d, 2H$_{Ar}$, *J*=8.0), 7.76 (d, 2H$_{Ar}$, *J*=8.0), 4.2 (q, -CH_3), 3.27 (s,-CH_2-), 1.36 (s,-CH_3), 1.22 (t,-CH_3)
$PhSO_2CH_2CN$	10.47 10.82	315.3 448.1 *315.0803* *448.1331*	57[a]	**Mono:** 7.38 (d, 2H$_{Ar}$, *J*=8.1), 8.12 (d, 2H$_{Ar}$, *J*=8.1), 7.61-7.85 (5H,Ar), 4.12 (dd, 1H, *J*=4.1, 11.75), 3.65 (dd, 1H, *J*=4.1, 13), 3.2 (dd, 1H, *J*=2, 13.58) **Bis:** DMSO-d_6 7.15-8.0 (9H, Ar), 3.2-3.5 (3H, -CH_2-, -CH)

[a,b]Represent the percentage purity of each compound based upon the HPLC area of the crude product. [b]The yield reported for diethyl methylmalonate, and ethyl 2-methylacetoacetate is after simple aqueous extraction, which removes a minor impurity present in the crude product. HPLC analyses were carried out on a Targa column (C18, 5 μ, 50×46 mm, Higgins Inc.) with a gradient of 5% acetonitrile elution in 0.1 M TEAA buffer (pH 7.0; sample injection size 20 μl) using a Perkin–Elmer Series 200 IC pump at a flow rate of 1 mL/min using a 235C diode array detector monitoring at 255 and 355 nm. Mass spectra analyses were obtained on a PE Sciex API-100 single quadropole mode with corona discharge and positive ion APCI at 400°C. Mass spectra for entries for 1 and 5 (shown in italics) were obtained with a Mariner instrument.

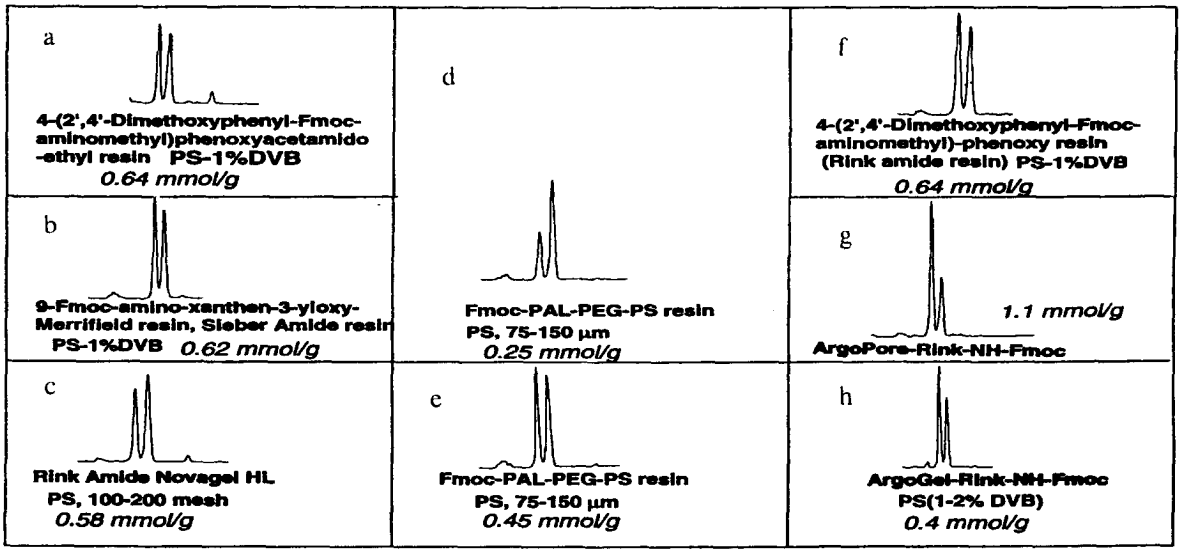


Figure 1. HPLC profiles of the product mixtures obtained from the reaction of diethylmalonate with the alcohol attached to various polymer supports

It must be noted that the bis-alkylated product is 133 amu higher than the desired product, which corresponds to the $NH_2COC_6H_5CH_2$- unit. After carefully reviewing all the reaction possibilities coupled with NMR and the mass data, we surmise that the bis-alkylkated product is generated from an intramolecular reaction/site–site interaction.

We believe that site–site interactions, due to increased local concentration of the reactive sites on the resin, could be the cause for the bis-alkylation. Based upon this assumption we anticipated that the use of lower loaded resin would provide mostly monoalkylated product. In order to probe this idea further we explored this reaction using various commercially available resins. Fig. 1 shows the HPLC profiles of the product mixture (in every case the bis-alkylated product is early eluting). It is evident that the resin with the higher loading such as Argogel Rink (1.1 mmol/g) afforded significantly higher bis-alkylated product, whereas PAL-PEG-PS resin (0.25 mmol/g) produced less of it (compare for example panels g and d in Fig. 1). However, none of these resins produced exclusively mono- or bis-alkylated product. Such a phenomenon in solid phase, though not very common, has been reported by Crowley et al.[15] In their study they have observed that the Dieckmann cyclization of alkyl sebacyl resin esters gave dimeric diketoesters resulting from site–site interaction along with the expected transesterification products. Hodge and Waterhouse have observed that the terephthaldehyde, upon reaction with polymer bound diol, gives both 'singly bound' and 'doubly bound' (both aldehyde groups are protected as acetals) products.[16,17] Also, Yang and Sun monitored the interaction between resin-bound reactive groups by measuring the single bead IR signals.[18]

In this initial study we have clearly demonstrated the usefulness of the Mitsunobu reaction in C–C bond formation. This study also highlights the inherent problem associated with solid phase chemistry in controlling the course of certain classes of reactions due to undesired site–site interaction. However, one can exploit this limitation to generate quaternary carbon centers starting with a mono-alkylated active methylene compounds (entries 2 and 4 in Table 1). Interestingly, controlling the quantity of the reagents in the Mitsunobu reaction also had little effect on the product ratio. For instance, use of 1.2 equivalents of all reactants and reagents produced the same product profile. However, the reaction was incomplete. Currently, our efforts are directed towards studying the effect of other parameters on the product ratios. For instance, initial experiments have revealed that the use of different solvents such as THF, DME, DMF, and DCM for the Mitsunobu reaction has very little (5–15%) effect on the product ratios. Reactions in the latter two solvents resulted in incomplete reaction.

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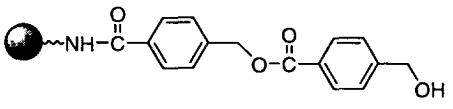
13. The syntheses were performed in a parallel array on a robotic liquid handler synthesizer (SOLARIS™). The additions, aspirations, and washings were performed using a robotic arm possessing four alternate aspirating and coaxial tips. The

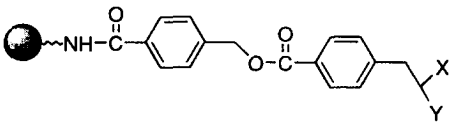
4-(2′,4′-dimethoxyphenylfluorenylmethoxycarbonylaminomethyl)phenoxy polystyrene, 'Rink Amide resin', loaded at 0.6 mmol Fmoc-amine/gm was placed in a round bottomed flask and was subjected to Fmoc cleavage with 20% piperidine in DMF for 10 min. The resin was subjected to a series of washings (3×5 mL) with DMF, MeOH, and DCM. Subsequently, the next step was coupling of the HMBA to the resin using 3 equivalents of DIC, HOBt, and HMBA in DMA for 4 h. At this stage, the solvent was drained and each flask was subjected to standard washing cycles. The next step was the Mitsunobu C–C alkylation using fivefold excess of tributylphosphine, *N,N,N′,N′*-tetramethylazodicarboxamide, and the active methylene compounds was conducted in dry THF at room temperature. After shaking the mixture for 12 h at room temperature, the reagents were drained and the resin was subjected to the washing cycles. Cleavage of products from the resin was performed with 20% TFA in DCM over 45 min at rt gave the desired compounds.

14. Structure of dimeric ester and the resultant Mitsunobu product product:

(a)



(b)



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