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Improved Procedure for the Purification of PEG Bound Molecules by the Use of Trioctylamine

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Abstract

The use of trioctylamine instead of triethylamine in reactions in which their hydrochlorides are formed simplifies purification and analytical procedures in the synthesis of small organic molecules on PEG supports.

Keywords: Soluble polymer-supported synthesis.

The use of polyethylene glycols (PEGs) as soluble polymeric supports for the synthesis of small organic molecules is currently receiving a great deal of attention [1,2]. Organic synthesis on these polymers profits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, analytical simplicity) and of solid phase methods (easy isolation and purification of the products) [1,2].

The purification step is generally carried out by simply precipitating the polymer by addition of a poorly polar solvent (typically Et_2O) followed by removal of unreacted material and by-products by filtration. A pre-requisite to the use of this methodology is the non-polymer bound species being readily soluble in Et_2O, and obviously this is not always the case. For instance, in the course of our studies on the PEG-supported synthesis of β-lactams [2] we observed that polar trialkylamine hydrochlorides such as Et_3N (TEA) hydrochloride were difficult by-products to dispose of during reaction work-up, and that this resulted in decreased isolated yields and complex, when not impossible, spectral analysis of the immobilized products (^1H NMR, IR). We report here that the simple replacement of TEA with the less polar trioctylamine (TOA) provides an easy solution to this problem [3].

The examples collected in the Scheme illustrate the scope of this finding. The mesylates of PEGs or of their monoethers are the commonest starting materials for PEG-supported synthesis, and must therefore be produced in large amounts and readily purified. The use of TOA instead of TEA as base in the mesylation reaction ($MeSO_2Cl$, CH_2Cl_2, RT) allowed us to consistently achieve quantitative yields of mesylates **1-4** and to avoid completely the need for

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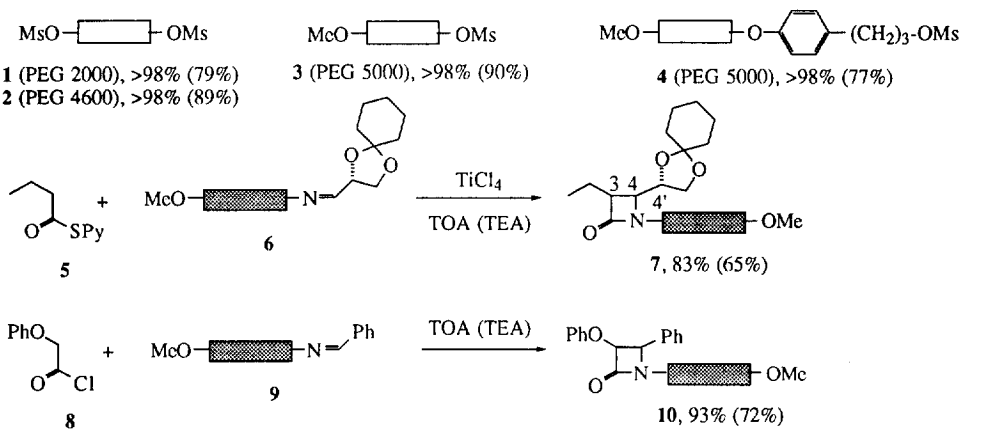
aqueous washing in the purification procedure which would leave behind difficult to remove traces of water in the hygroscopic PEG. Yields with TEA are reported in parentheses.

TOA proved to be more convenient than TEA also for the generation of reactive species to be coupled with PEG-supported substrates. Thus, *S*-2-pyridylthiobutanoate **5** (7 mol equiv/mol equiv of imine) was transformed into its trichlorotitanium enolate [2] by the addition of $TiCl_4$ and TOA and reacted (-78 to 20°C, CH_2Cl_2) with the (*R*)-glyceraldehyde derived imine **6** [4] to give the corresponding β-lactam **7** in 83% isolated yields (65% with TEA). Similarly, TOA was used to transform phenoxyacetyl chloride **8** to the corresponding ketene (15 mol equiv/mol equiv of imine) that was reacted (CH_2Cl_2, RT) with imine **9** to give the β-lactam **10** in 93% isolated yield (72% with TEA). Furthermore, when both **7** and **10** were synthesized using TOA their ^1H NMR analysis could be easily carried out on the precipitated products to assess their diastereoisomeric ratios (d.r.)§. This was impossible when TEA was used, since the large amounts of TEA·HCl that co-precipitated with PEG hampered the d.r. determination.

In conclusion, the use of a more lipophilic and less polar reagent provided a simple way to circumvent a purification problem associated with PEG-supported synthesis. We believe that extension of this approach to other reagents employed in this context can also be effective.

Scheme.



Abbreviations: Ms = $MeSO_2$; Py = 2-pyridyl; ▭ = $(CH_2CH_2O)_n$; ▩ = $(CH_2CH_2O)_n$-Ph-$(CH_2)_3O$-Ph

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§ **7**: (3*S*,4*R*,4'*S*)/(3*R*,4*R*,4'*S*) = 60/40; the configuration was assigned by comparison of ^1H NMR data of the β-lactam removed ($Ce(NH_4)_2(NO_3)_6$, MeCN, water) from the polymer [5]. **10**: 3,4-*cis*/3,4-*trans* = >98/2 (J *cis* = 5.0 Hz; J *trans* 2.0 Hz).