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# Solid-phase synthesis of functionalized tropane derivatives via 1,3-dipolar cycloaddition

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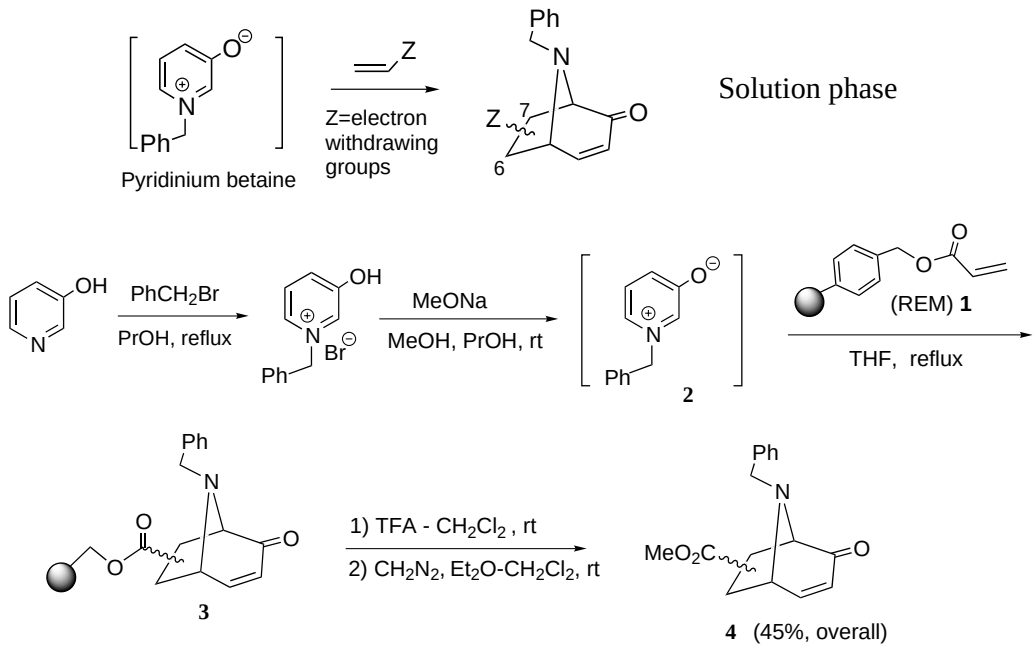
**Abstract**—1,3-Dipolar cycloaddition of 3-oxidopyridinium betaine to activated olefins on solid-phase leads to resin-bound 8-azabicyclo[3.2.1]octenones which undergo further transformations such as 1,4-addition of nucleophiles. Cleavage of benzyl linker is achieved using acid chlorides in the presence of potassium iodide to give substituted tropane derivatives. 

The tropane ring system is found in numerous naturally occurring alkaloids, many of which possess potent biological activity such as atropine, scopolamine and cocaine.[1] Although many synthetic methods are available for the preparation of this structural component in solution phase,[2] their extension to solid-phase synthesis and chemical library production[3] has been very limited. Until now, only two reports on the solid-phase chemistry of tropane derivatives are known. In an interesting revisitation of the classical Robinson tropinone synthesis, a solid-phase version has been developed, which involved reacting a resin-bound ε-amine of lysine with succinic dialdehyde and 1.3-acetonedicarboxylic acid.[4] In the second report, an already prepared tropane scaffold was attached to dihydropyran linker, followed by subjection to further transformations.[5]




**Scheme 1.**

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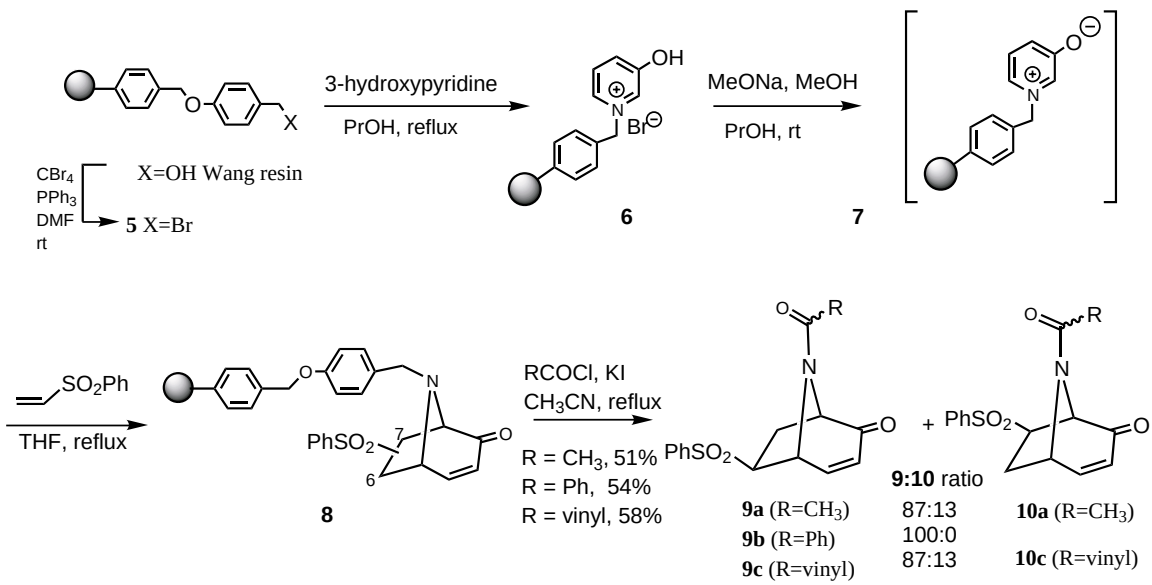
1,3-Dipolar cycloaddition of pyridinium betaine to activated alkenes, initially developed by Katritzky et al., provided one of the most powerful and versatile tools for the construction of 8-azabicyclo-[3.2.1]octane derivatives.[6] We describe herein the first application of this method to solid-phase synthesis of tropane derivatives.

To demonstrate the feasibility of this reaction, the commercially available and easily cleavable REM resin (hydroxymethyl polystyrene resin-bound acrylate) **1**[7] was first used. Treatment of this resin with excess (6 equiv.) 3-oxidopyridinium betaine **2**, readily prepared from 3-hydroxypyridine, in refluxing THF for 36 h gave the polymer-bound α,β-unsaturated ketone **3** [IR (KBr): $\nu_{max}$ 1731, 1690 $cm^{-1}$] (Scheme 1).[8] In order to determine the regio- and stereoselectivity of this solid-phase [3+2] cycloaddition reaction, the polymer bead was subjected to the cleavage conditions. To this end, stirring ketone **3** in trifluoroacetic acid (TFA)–$CH_2Cl_2$ (1:3) for 1 h at room temperature furnished, after treatment with diazomethane, the 8-azabicyclo[3.2.1]octane derivative **4** in 45% overall yield on the basis of the initial loading level of REM resin. This product was found to be a mixture of four regio- and stereoisomers in 50:25:20:5 ratio.[9,10] These selectivities are comparable to those observed for the analogous reaction in solution.[11]

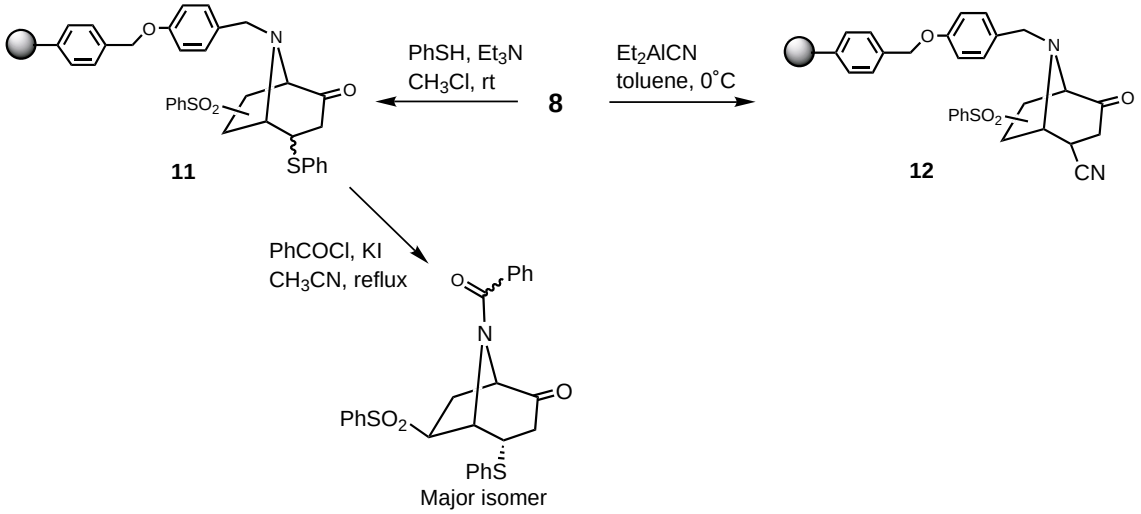
We turned next to the 1,3-dipolar cycloaddition of the polymer-supported betaine **7** to phenyl vinyl sulfone. In fact, it was established that in contrast to methyl acrylate, the reaction with phenyl vinyl sulfone in solution was highly regio- and stereoselective, and led to the 6-*exo*-sulfone in good overall yield.[12,13] This sequence began with the bromomethyl linker **5** obtained by bromination of Wang resin ($CBr_4$, $PPh_3$, DMF).[14] Reaction of **5** with 3-hydroxypyridine in refluxing propanol for 30 h gave the polymer-bound 3-hydroxypyridinium bromide **6** [IR (KBr): $\nu_{max}$ 3318 $cm^{-1}$], which was treated with sodium methoxide (MeONa) in propanol to afford **7** (Scheme 2). This resin-bound betaine, readily isolated by washing with propanol and drying under vacuum, was immediately subjected to 1,3-dipolar cycloaddition conditions. Heating **7** in the presence of excess phenyl vinyl sulfone (6 equiv.) in THF at refluxing temperature for 16 h led to resin-bound cycloadduct **8** [IR (KBr): $\nu_{max}$ 1691 $cm^{-1}$].[15]

While releasing bicyclic enone **4** from the resin was straightforward, the benzyl linker in **8** has been found to be very stable towards a variety of cleavage conditions. First attempts using acidic (TFA, pure or as a solution in $CH_2Cl_2$, for 1 h to 3 days) or oxidative [2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene or in $CH_2Cl_2$–$H_2O$,[16] ceric ammonium nitrate (CAN) in $CH_3CN$–$H_2O$] conditions were disappointing. Under these conditions the cleavage was incomplete releasing the tropane derivative in low yield. After extensive experimentations, the best results have been found when **8** was treated with acid chlorides in acetonitrile in the presence of potassium iodide.[17] Thus heating **8** with acetyl chloride (7.5 equiv.) and potassium iodide (5 equiv.) in refluxing acetonitrile for 6 h furnished a separable mixture of amides **9a** (6-*exo* sulfone) and **10a** (7-*exo* sulfone) (87:13 ratio) in 51% overall yield on the basis of the initial loading level of resin.[18,19] The use of KI in this reaction was crucial, otherwise the cleavage was inefficient. When acetyl chloride was replaced by benzoyl chloride, only the 6-*exo* isomer **9b** can be isolated in 54% overall yield. The cleavage using acryloyl chloride led to a separable mixture of amides **9c** and **10c** in a similar ratio as with acetyl chloride in 58% overall yield (Scheme 2).

The success of this reaction prompted us to explore further transformations on the resin-supported 8-azabicyclo[3.2.1]octenone **8** (Scheme 3). 1,4-Addition of thiophenol was first attempted. Stirring of **8** with thiophenol and triethylamine in chloroform at room temperature for 20 h led to **11** as shown from the IR spectrum [IR (KBr): $\nu_{max}$ 1728 $cm^{-1}$]. Cleavage of the product from the solid support was readily achieved using benzoyl chloride–potassium iodide in refluxing acetonitrile. As in solution




**Scheme 2.**




**Scheme 3.**

phase,[10] the crude product was found to be a mixture of 4-*endo* and 4-*exo* isomers (7:3) as shown from $^1$H NMR analysis.[20] Next, the resin-bound enone **8** was treated with diethylaluminum cyanide ($Et_2AlCN$) in toluene at 0°C for 4 h. As above, the IR spectrum of the resin **12** showed the complete disappearance of the enone band and the presence of absorbances at 1731 cm$^{-1}$ (CO) and 2244 cm$^{-1}$ (CN).

In conclusion, we have successfully implemented 1,3-dipolar cycloaddition of 3-oxidopyridinium betaine to activated olefins on solid-phase. Cleavage of tropane derivatives using acid chlorides–KI was achieved in good overall isolated yield. Furthermore, we have shown that the formed resin-bound 8-azabicyclo[3.2.1]octenone may undergo further transformation such as 1,4-addition of nucleophiles affording substituted tropane derivatives.

## Acknowledgements

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8. $^1$H NMR analysis of this polymer revealed the presence of about 10% unreacted starting REM resin, despite the use of a large excess of betaine.
9. This 6,7, *exo*:*endo* ratio (6 *exo*/6 *endo*/7 *exo*/7 *endo*: 50/25/20/5) was determined using 400 MHz $^1$H NMR of the mixture, after flash column chromatography.
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15. $^1$H NMR analysis of this resin seemed to be in agreement with structure **8**, which was confirmed after cleavage.
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18. According to $^1$H and $^{13}$C NMR spectra, each of these isomers was found to be a mixture of atropoisomers.
19. IR analysis of polymer recovered from the cleavage reaction shows complete disappearance of the carbonyl absorbance of the enone (1691 cm$^{-1}$).
20. Only the major isomer was isolated and the *endo* configuration was assigned from its 400 MHz $^1$H NMR spectrum. As for compounds **9** and **10**, this product was found to be a mixture of atropoisomers