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Preparation and evaluation of a polymer-supported Mukaiyama reagent

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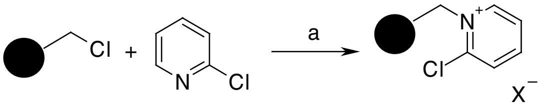
Abstract—The synthesis of a polymer-supported Mukaiyama reagent is described. This preparation was thoroughly optimized using a DoE approach to achieve optimum loading, and the procedure was successfully applied to prepare the supported reagent on a 10 g scale. This reagent proved to be effective for the formation of carbodiimides through the dehydration of thioureas and for a one-pot guanylation of primary amines.

1. Introduction

2-Chloro-1-methylpyridinium iodide (known as the Mukaiyama reagent) has gained a lot of interest in organic synthesis as it can be used as an acid-activating agent[1] or for the preparation of carbodiimides[2] and guanidines.[3] However, Mukaiyama reagent is quite insoluble in most standard organic solvents and the side-product of the reaction is generally hard to remove by chromatography. These limitations have restricted the practical application of this reagent. Therefore, we decided to prepare a polymer-bound variant of Mukaiyama reagent.

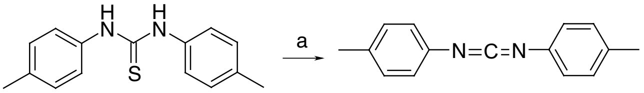
This paper describes the preparation of a polymer-supported (PS) Mukaiyama reagent by reaction of Merrifield's resin and 2-chloropyridine in the presence of potassium iodide (Scheme 1) and the subsequent determination of resin loading. Results are also presented that demonstrate that this polymer-supported reagent can be used for the efficient formation of carbodiimides through the dehydration of thioureas and for the guanylation of primary amines.



Scheme 1. (a) KI, DMF, 60 °C.

2. Results and discussion

To determine the resin loading a suitable 'end-use' assay was devised. The reaction chosen for this purpose was the dehydration of 1,3-di-(*p*-tolyl)thiourea, as described by Mukaiyama.[4] The yield for this reaction is 97% according to the publication. Thus the 'end-use' assay to determine the loading of the resin consisted of the dehydration of 1,3-di-(*p*-tolyl)thiourea in the presence of an internal standard. The extent of the reaction was measured by LC–MS analysis to give the ratio of residual thiourea to 3-acetylacetanilide (used as an internal standard) and allowed calculation of the loading. This test reaction was repeated in solution, in the presence of the standard 3-acetylacetanilide in order to check that there was no interference with the reaction (Scheme 2). To circumvent any potential solubility issues, it was decided at this stage to perform the reaction in DMF. The reaction was complete after 30 min at



Scheme 2. (a) Mukaiyama reagent, 3-acetylacetanilide, DMF, Et_3N, rt.

Keywords: Mukaiyama reagent; Carbodiimide; Guanidines.

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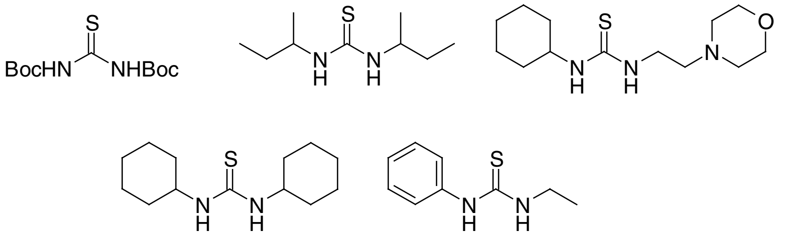
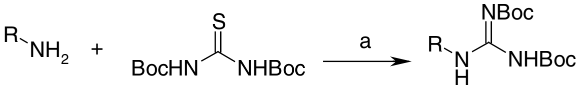


Figure 1.

rt using 1.2 equiv Mukaiyama reagent and 2.4 equiv triethylamine. The expected carbodiimide was then isolated in 91% yield.

The conditions used for the first experiments to prepare PS-Mukaiyama reagent were 2 equiv of 2-chloropyridine, 2 equiv of potassium iodide in DMF, overnight at 60 °C in a rotating oven, with Merrifield's resin at 3 mmol/g. In order to determine the best conditions for this preparation, a design of experiments (DoE) approach using the MODDE software from Umetrics was employed.[5] Experiments were designed, which investigated the following parameters: equivalent of 2-chloropyridine, equivalent of KI, solvent (DMF, *N*,*N*-DMA, NMP), temperature and reaction time. The 'end-use' assay was then performed in order to determine the loading of these batches of resin. The optimal conditions for the PS-Mukaiyama reagent preparation were determined to be 2 equiv of 2-chloropyridine, 1 equiv of KI in DMF at 40 °C for 24 h.[6] These conditions gave a resin loading of 1.33 mmol/g (72%). A lower loading sample of Merrifield's resin (1.5 mmol/g) was also used as starting material in order to compare the loading of the resulting resins. The 'end-use' assay performed on this batch revealed a loading of 0.38 mmol/g (33%). It was thus decided to use the Merrifield's resin at 3 mmol/g. A batch of 3 g of resin was then prepared under the optimized conditions, overnight using the rotating oven. The loading was then determined to be 1.02 mmol/g (55%). As this loading was lower than expected, the scale-up of this reaction was investigated further. It was found that good agitation during the reaction was crucial in order to get a good loading. A 10 g batch was then prepared in a round-bottom flask using an overhead stirrer, and the resin loading was determined to be 1.2 mmol/g (65%).

Once the optimum conditions for the preparation of the polymer-supported Mukaiyama reagent were established, it was then decided to test this reagent for thiourea dehydration. During the 'end-use' assay, dehydration of 1,3-di-(*p*-tolyl)thiourea with 1.2 equiv of PS-Mukaiyama reagent was not complete. The reaction was then repeated with 5 equiv of resin and the reaction was complete after 16 h at rt. The crude material was contaminated by a triethylamine salt: after a quick water wash the clean carbodiimide was isolated in 84% yield.[7] Dehydration of a range of thioureas was then investigated (Fig. 1). Different work-up conditions were tried in order to remove the triethylamine salt impurity (wash with water, wash with a saturated bicarbonate solution and use of carbonate resin) but in all cases a loss of product mass was observed and the carbodiimide was partially decomposed.



Scheme 3. (a) PS-Mukaiyama reagent, DMF, Et_3N, rt.

This new PS-Mukaiyama reagent was then investigated as a reagent for the one-pot guanylation of amines with di-Boc-thiourea. Such reactions have already been carried out using Mukaiyama reagent in solution.[3] It was considered that the use of a PS-Mukaiyama reagent would avoid any purification by chromatography as the product would be isolated by simple filtration. At first guanylations were accomplished with the same amines (**1a**–**d**) as in the Lipton paper,[3] using 1.2 equiv of resin at rt overnight (Scheme 3, Table 1). Except for benzylamine **1a**, the conversions of these reactions were modest. Increased amounts of resin and longer reaction times did not improve these results. It was concluded that PS-Mukaiyama reagent is not convenient for the guanylations of secondary amines. A range of primary amines (**1f**–**j**) was then investigated in order to determine the scope of the method (Table 2). The reaction did not work at all with ammonia **1j**, and the conversion was poor with very hindered amines such as aminodiphenylmethane **1h**. Reactions proceeded in good yield with the other substrates.[8] As a water wash was necessary to remove the triethylamine salt, sometimes some product was lost during the work-up. In order to avoid any wash whatsoever, guanylation with benzylamine was repeated with potassium carbonate instead of triethylamine as a base.[9] In that case, the crude product was taken up in DCM and filtered through a plug of silica. Clean product **2a** was then isolated in 74% yield.

3. Conclusion

In the course of our investigations we have successfully prepared a polymer-supported Mukaiyama reagent with a good loading. This preparation was thoroughly optimized using a DoE approach and the procedure was successfully applied to prepare the resin on a large scale (10 g). This reagent was then successfully used for the

Table 1

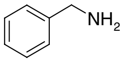
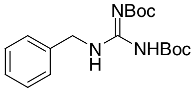
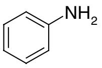
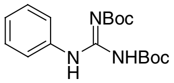
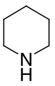
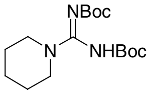
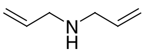
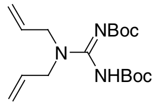
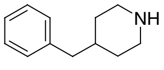
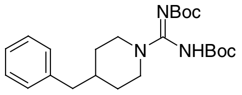
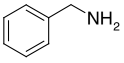
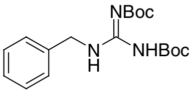
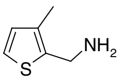
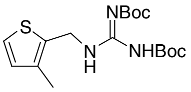
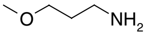
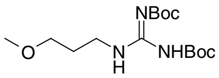
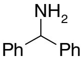
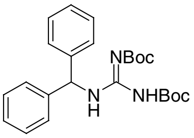
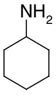
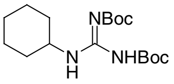
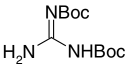
	Amine	Product		Conversion (%)	Litreature yield[3] (%)
1a			**2a**	100 (92% yield)	91
1b			**2b**	16	34
1c			**2c**	11	57
1d			**2d**	33	86
1e			**2e**	25	—

Table 2

	Amine	Product		Yield (%)	Purity (%)[a]
1a			**2a**	92	100
1f			**2f**	70	93
1g			**2g**	100	92
1h			**2h**	16	—
1i			**2i**	46	100
1j	NH_3		**2j**	3	—

[a] Purity was determined by HPLC using UV detection at 215 nm.

formation of carbodiimides through the dehydration of thioureas and for the guanylation of primary amines.

References and notes

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4. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*(10), 707–721.
5. For further information see www.umetrics.com
6. PS-Mukaiyama reagent preparation: Merrifield's resin 3 mmol/g (500 mg, 1.5 mmol) was swollen in 5 ml of DMF in a fritted syringe. 2-Chloropyridine (3 mmol) and potassium iodide (1.5 mmol) were then added. The reaction mixture was rotated at 40 °C for 24 h, then filtered and washed with DMF, DCM, MeOH (3 ×). Drying under high vacuum at 40 °C afforded the PS-Mukaiyama reagent.
7. Data for di-(*p*-tolyl)-carbodiimide: ^1H NMR (250 MHz, $CDCl_3$) δ: 7.13 (d, 4H, $J = 8.2$ Hz), 7.07 (d, 4H, $J = 8.2$ Hz), 2.34 (s, 6H, Me). LC–MS: calcd for $C_{15}H_{14}N_2$: 222.29. Found 223.23 $(M+H)^+$. IR: 2118, 2098 cm^{-1}.

8. Guanylation procedure with triethylamine as a base: PS-Mukaiyama reagent (0.24 mmol) was swollen in 1.5 ml of DMF in a fritted syringe. Triethylamine (0.44 mmol), thiourea (0.24 mmol) and amine (0.2 mmol) were then added. The reaction mixture was rotated at rt for 24 h, then filtered and evaporated. The crude material was taken up in 2 ml of DCM, washed with water (3 × 2 ml). Drying over $MgSO_4$, filtration then evaporation afforded the clean product. Data for guanidine **1a**: ^1H NMR (250 MHz, $CDCl_3$) δ: 11.54 (br s, 1H, NH), 8.58 (br s, 1H, NH), 7.37–7.28 (m, 5H, Ph), 4.63 (d, 2H, CH_2Ph, $J = 5.12$ Hz), 1.52 (s, 9H, *t*-Bu), 1.48 (s, 9H, *t*-Bu). LC–MS: calcd for $C_{18}H_{27}N_3O_4$: 349.43. Found 350.47 $(M+H)^+$, 294.43 $(M+H-t\text{-Bu})^+$.
9. Guanylation with potassium carbonate as a base: PS-Mukaiyama reagent (0.24 mmol) was swollen in 1.5 ml of DMF in a fritted syringe. Potassium carbonate (0.44 mmol), thiourea (0.24 mmol) and amine (0.2 mmol) were then added. The reaction mixture was rotated at rt for 24 h, then filtered and evaporated. The crude material was taken up in DCM and filtered through a plug of silica. Evaporation afforded the clean product.