Application of Piperazine-Derived Hydrazone Linkers for Alkylation of Solid-Phase Immobilized Ketones

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Abstract: The preparation and application of three new solid supports with piperazine-derived hydrazine anchoring groups are described. The supports were used for immobilization of ketones. The ketones: cyclohexanone, 4-*tert*-butylcyclohexanone, 3-pentanone and tropinone, which were bound to polymers in the form of their hydrazones, were deprotonated with LDA and alkylated with propyl iodide or benzyl bromide. The resulting alkylated products were cleaved off the solid support on treatment with trifluoroacetic acid in dichloromethane. Linkers with 6- and 3-carbon atom spacers gave better results than the simple *N*-aminopiperazine linker.

Key words: alkylations, hydrazones, ketones, lithiation, solid-phase synthesis

Alkylation of ketones is one of the well-established strategies for C–C bond construction in organic synthesis. One of the powerful tools for such transformation is alkylation of the corresponding ketone hydrazones acting, as synthetic equivalents of ketones.[1] Alkylation of ketones on solid-phase could be an important tool in combinatorial chemistry.[2] To the best of our knowledge no alkylation of ketone hydrazones on solid support has been reported. Anchoring of ketones and aldehydes to solid-phase has been realised through formation of acetals,[3] semicarbazones,[4] thioacetals,[5] hydrazones[6] and imines.[7] The aldehyde hydrazones were recently used in solid-phase synthesis of secondary amines.[8] In this letter, we wish to present a method for simple and efficient preparation of polymer supports with a hydrazine anchoring group for reversible binding of ketones in the form of their hydrazones and application of such supports for alkylation of ketones in solid-phase organic synthesis.

Although the most often used hydrazones for alkylation of ketones are *N*,*N*-dimethylhydrazones, we have decided to use piperazine as a bifunctional scaffold for the new linker. Since deprotonation/lithiation followed by alkylation of hydrazone is typically done at low temperatures and requires relatively long reaction times we have decided also to investigate possible effect of a 6- and 3-carbon atom spacer for efficiency of the alkylation process. We reasoned that such spacers should add flexibility to the linker groups and facilitate accessibility of polymer bound substrates to aggregated species of lithium amide bases[9] as well as the lithiated hydrazones to alkylating reagents.

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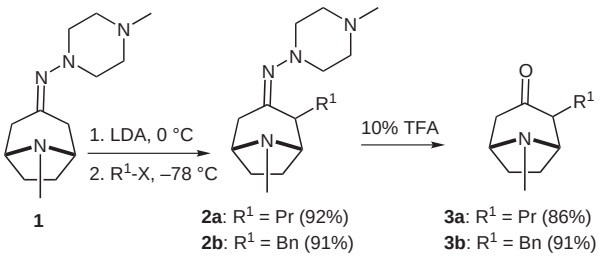
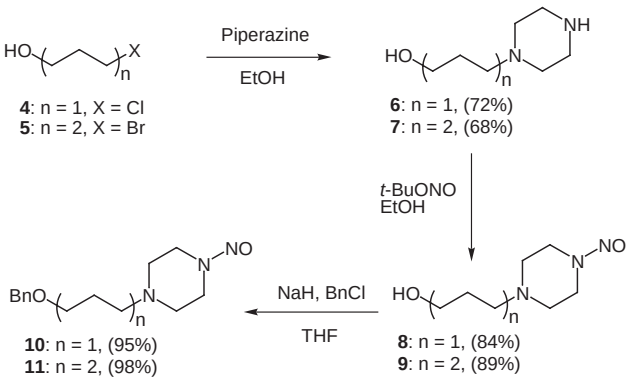
Reactions in Solution

In order to probe the suitability of piperazine derived hydrazones as linkers for alkylation of ketones on solid-phase we investigated the process of alkylation and cleavage in solution (a representative example is shown in Scheme 1). The ketone hydrazones were prepared by heating 1-amino-4-methylpiperazine with 3-pentanone, cyclohexanone, 4-*tert*-butylcyclohexanone, and tropinone (8-methyl-8-azabicyclo[3.2.1]octan-3-one) respectively. Deprotonation of the resulting hydrazones with LDA under typical conditions[10] followed by alkylation with alkyl halides gave hydrazones, which were isolated and subjected, without purification, to cleavage. After some experimentation with several aqueous acids (hydrochloric, citric, oxalic, and acetic acid) we found that trifluoroacetic acid (TFA) gave clean and complete cleavage in short time (30 min). Overall, the alkylated ketones were obtained in good yields (Scheme 1) and in high purities (GC analysis).



Scheme 1

The synthesis of linkers with hydrazine group and 3- or 6-carbon atom spacer started with preparation of hydroxy nitrosoamines **8** and **9** from readily available materials (Scheme 2). The alkylation of piperazine with 3-chloropropan-1-ol and 6-bromohexan-1-ol provided **6** and **7** in good yields. Nitrosation of the hydroxyalkylpiperazines under optimised conditions (42 ºC, ethanol, 1.5 equiv *t*-BuONO) gave nitrosoamines[11] **8** and **9**. The attachment of the *N*-nitrosoamine precursors of hydrazines to the Merrifield polymer was tested through reaction with benzyl chloride. The O-benzylation of **8** and **9** under optimised conditions (NaH, 2-fold excess of alcohol, reflux in THF) was regioselective and gave the expected products **10** and **11** in excellent yields (Scheme 2). In contrast reactions of aminoacid-derived analogues: *N*-nitroso-(3-hydroxypro-

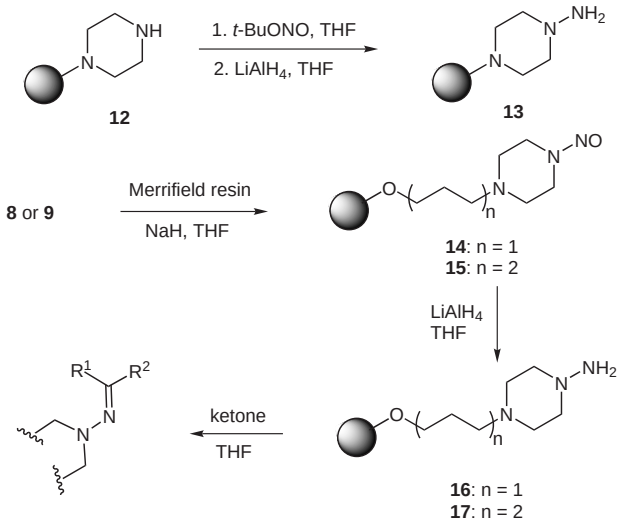


Scheme 2

pyl)methylamine and *N*-nitroso-(6-hydroxyhexyl)methylamine with benzyl chloride under optimised conditions gave only 50–60% yields of O-benzylation.

Preparation of Polymeric Supports

The simple polymeric support with hydrazine anchoring group **13** was prepared by nitrosation of piperazinomethylpolystyrene[12] **12** followed by reduction of the resulting nitrosoamine with $LiAlH_4$ (Scheme 3).

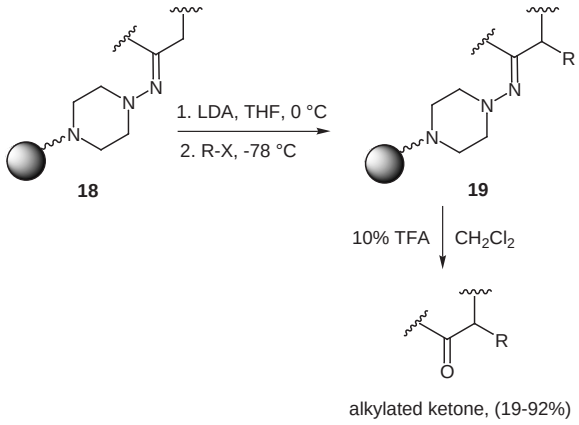


Scheme 3

The polymers with the spacer-modified linkers were prepared by the reaction of alcohols **8** and **9** with Merrifield resin followed by reduction.[13] The loading of hydrazine groups on these polymers[14] (determined from mass of the attached ketone or amine hydrochloride[15]) indicated that the preparation of resin **13** was modestly efficient (38% of the theoretical loading) while the formation of resins with spacers was fairly efficient (58% and 68% over two steps; based on theoretical loading). The low yield of formation of **13** was probably caused by low selectivity of the nitrosation of polymer bound piperazine. The stability of the polymer bound hydrazines under inert gas atmosphere in the refrigerator is good; however on prolonged storage (few months) significant deterioration of their loadings was observed.

Alkylation of Ketones on Solid Support

The ketone substrates were attached to the hydrazine resin by heating the resin with excess of the ketone in anhydrous THF overnight. The resulting polymer bound hydrazones were deprotonated/lithiated with excess of LDA in THF for 6 hours at 0 °C (Scheme 4). The resulting lithiated hydrazones were alkylated with propyl iodide or benzyl bromide at –78 °C for 14 hours. The alkylated products were cleaved off the resin with 10% solution of TFA in dichloromethane. The products alkylated on polymers with spacer-modified linkers were obtained in good yields (based on the loadings of substrates) and high purities (Table 1).[16] However the alkylation of ketones (e.g. cyclohexanone) on support **13** gave only low yield of very impure products.



Scheme 4

The effect of the 6- and 3-carbon atom spacer is similar with slight superiority of the longer chain. However preparation of the precursor of the ‘C-3 hydrazine linker’ **8** is based on cheaper starting material. Therefore, this resin should be preferred by cost conscious users.

In summary, two novel hydrazine resins (‘C-3 hydrazine’ and ‘C-6 hydrazine’) derived from readily available materials can be used for immobilization of ketones in the form of hydrazones.[17] The polymer bound ketone hydrazones can be alkylated under typical conditions and cleaved off the supports with moderately strong acid. The overall process gives a reliable method for alkylation of ketones in SPOS and may find use in combinatorial chemistry.

Table 1 Alkylation of Ketones on Solid-Phase through Hydrazone Linker Strategy

Entry	Resin	Ketone (loading of starting hydrazine, mmol/g)	R–X	Yield of alkylation (purity[a])
1	**17**	3-Pentanone (0.58)	Pr–I	82 (85%)
2	**17**	3-Pentanone (0.58)	Bn–Br	91 (83%)
3	**17**	Tropinone (0.57)	Pr–I	74 (90%)[b]
4	**17**	Tropinone (0.57)	Bn–Br	54 (91%)[c]
5	**17**	4-*t*-Bu-cyclohexanone (0.59)	Pr–I	82 (81%)[d]
6	**17**	4-*t*-Bu-cyclohexanone (0.59)	Bn–Br	74 (86%)[e]
7	**17**	Cyclohexanone (0.59)	Pr–I	92 (93%)
8	**17**	Cyclohexanone (0.59)	Bn–Br	84 (96%)
9	**16**	Cyclohexanone (0.52)	Pr–I	70 (85%)
10	**16**	Cyclohexanone (0.52)	Bn–Br	88 (86%)
11	**13**	Cyclohexanone (0.38)	Pr–I	26 (63%)
12	**13**	Cyclohexanone (0.38)	Bn–Br	19 (68%)

[a] Purities of the products were measured by GC/MS analysis.
[b] Mixture of diastereomers 30:1. [c] Mixture of diastereomers 32:1.
[d] Mixture of diastereomers 3:1. [e] Mixture of diastereomers 11:3.

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(11) CAUTION: *N*-Nitrosoamines are potentially carcinogenic. Therefore we recommend special caution during handling and preparation.

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(13) **Procedure for Reduction of Nitrosoamine to Hydrazine on Polymeric Support:** The resin **14** (2.175 g, 2 mmol, theoretical loading 0.95 mmol/g, prepared from Novabiochem Merrifield polymer HL, 1.10 mmol/g, 1% DVB, 200-400 mesh), swollen in anhyd THF (15 mL) was heated with LAH (0.46 g, 12 mmol) under argon atmosphere to 55 ºC for 48 h. Then the reaction mixture was treated carefully with NH_3 aq and KOH aq to decompose the grey suspension of LAH. The resulting white precipitate was dissolved and removed by washing with 2 M HCl aq. The resin was washed with a mixture of concd HCl and THF (4.5:5.5, 2 × 10 mL), repeatedly with THF, methanol, dichloromethane followed by 10% (v/v) solution of triethylamine in dichloromethane (3 × 8 mL, under argon) and repeatedly with methanol and dichloromethane. The resulting resin was dried under high vacuum to constant mass (2.130 g, 93%).

(14) Microanalytical data (% of N) did not always show accurately the loading of hydrazine or hydrazone on the resins. Therefore a better method based on gravimetric measurement was developed.[15] The results of loading determinations based on $Et_3N{\cdot}HCl$ and *t*-butylcyclohexanone were usually in good agreement.

(15) **Procedure for Determination of Loading of Hydrazine on Polymeric Support:** (a) Based on amine hydrochloride: The resin **17** (0.500 g) was washed twice with a solution of aq concd HCl in THF (v/v 4.5:5.5) and washed repeatedly with THF, methanol and dichloromethane. Then the resin was washed three times with a 10% (v/v) solution of triethylamine in dichloromethane and repeatedly with methanol and dichloromethane. The combined amine solutions were concentrated and the residue was dried under vacuum to give white crystalline solid, $Et_3N{\cdot}HCl$ (0.122 g, 0.59 mmol/g). (b) Based on 4-*t*-butylcycohexanone(**20**): The resin **17** (0.500 g) was swollen in a solution of **20** (0.462 g, 3 mmol) in THF (5 mL) and heated in the presence of molecular sieves 4 Å under reflux over 12 h. Then the sieves were removed with tweezers and the resin was washed repeatedly with THF and ether. Then the resin was washed three times with 10% (v/v) solution of TFA in dichloromethane and repeatedly with methanol and dichloromethane. The combined acid solutions were washed with aq K_2CO_3, dried, and concentrated under moderate vacuum to give crystalline solid (0.045 g, 0.58 mmol/g).

(16) **Typical Procedure for the Alkylation of a Ketone on Solid-Phase:** The resin **17** (0.500 g, 0.295 mmol, 0.59 mmol/g, prepared from Novabiochem Merrifield polymer HL, 1.10 mmol/g, 1% DVB, 200-400 mesh) loaded with cyclohexanone was washed under argon atmosphere with anhyd THF (2 × 3 mL). The resin was cooled to 0 ºC for

10 min and treated with a solution of LDA in THF (3.60 mL, 0.98 M, 12 equiv) for 6 h. The resulting deep red resin was filtered under argon, cooled to –78 ºC, and treated with solution of propyl iodide (0.591 g, 0.34 mL, 3.55 mmol) in THF (3 mL). The reaction mixture was allowed to warm up slowly to r.t. over 14 h and was quenched with water (1 mL). The resin was washed repeatedly with THF, ether, dichloromethane and twice with 10% (v/v) TFA in dichloromethane followed by methanol and dichloromethane. The combined acidic solutions were washed with aq K_2CO_3, dried ($MgSO_4$) and concentrated to give 2-propylcyclohexanone (0.038 g, 92%).

(17) Structures of all new compounds were confirmed by spectrometric analyses and structures of polymers by IR and gel-phase ^{13}C NMR spectroscopy.