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Synthesis of polymeric supports with spacer-modified triazene linkers: aldol and Grignard reactions of immobilized nortropinone

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Abstract—Four new polymeric supports with 3- and 6-carbon atom spacers and triazene linkers derived from *meta-* and *para-*aminophenol were synthesized from commercial Merrifield polymer. The supports could be used for immobilization of secondary amines in SPOS. A new strategy based on the use of diethylamine triazenes as masked precursors for the generation of polymer-supported diazonium ions was used. The performance of the new linkers was tested on Grignard and aldol reactions of solid-phase immobilized nortropinone. The new supports with C₃-T2 linkers gave products with better yields and purities than the classical T2 supports or the supports with the C₆-T2 linkers. © 2003 Elsevier Science Ltd. All rights reserved.

The development of solid-phase organic synthesis (SPOS) methodology has been driven by the growing importance of combinatorial chemistry methods in the process of drug development.¹ The triazene based linkers² are one of the recent and fast growing additions to SPOS methodology. The so-called T2 linker originally introduced for anchoring secondary amines^{2a} has been used for synthesis of a number of different classes of compounds (amides, thioureas, ureas, hydrazines, alcohols, esters, guanidines, sulfoximines and alkyl halides).^{2b} We planed to use a triazene linker for immobilization of nortropinone, an important scaffold in medicinal chemistry, followed by reactions involving use of lithium amide bases and organomagnesium reagents. However we found that *n*-butyllithium or Grignard reagents complex or react with triazenes giving only low yields of products of addition to the carbonyl group of the triazene protected amino ketones (e.g. nortropinone).³ Reactions of LDA with triazenes were also reported recently.⁴ Therefore, we decided to synthesize modified triazene linkers. Herein, we report simple syntheses of supports with triazene linkers modified with 3- and 6-carbon atom spacers and a new strategy for the generation of supported diazonium ions, i.e. directly from triazenes.

Model studies in solution: In order to evaluate the stability of the new linkers under the conditions of lithium amide deprotonation, five model triazenes were synthesized (Scheme 1). The triazenes 1a and 2a were stirred with LDA in THF at -78°C for 6 h without any detectable decomposition. However, triazenes 1b and 2b showed slight decomposition at this temperature and all triazenes significantly decomposed after 8 h at 0°C. Similar treatment of these triazenes with a Grignard reagent (EtMgBr) at 0°C did not cause any detectable decomposition. The recent reports of based-induced fragmentation of 1-aryl-3,3-dibenzyltriazenes⁴ forced us to re-examine our preliminary results. In our hands, however, no alkylation of diethylamine triazene 3 or models 1a and 2a after reaction with n-BuLi in THF for 2 h at -78°C followed by treatment with methyl iodide could be observed. We could not detect any product of addition of lithiated diethylamine triazene 3 to the aldehyde after treatment of 3 with *n*-BuLi for 2



Scheme 1.

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h at -78° C followed by addition of benzaldehyde and quenching. These observations suggest that the triazenes without benzyl groups should be stable under the typical conditions of lithium amide deprotonation and to Grignard reagents.

Preparation of polymers: The amines were anchored to a T2-type polymeric support via reaction with a polymer bound diazonium ion. An aminophenol was typically used as the diazonium ion precursor.^{2a} We prepared *m*-aminophenol-derived precursors of the triazenes with added spacers **6** by alkylation of *m*-aminophenol with 3-chloropropan-1-ol or 6-bromohexan-1-ol followed by binding the resulting amino alcohols **5** to chloromethylpolystyrene by the Williamson reaction (Scheme 2). The amino groups of the resulting polymers **6** (isolated in the form of hydrochlorides) were transformed into diazonium ions upon treatment with *t*-BuONO at -18° C in dichloromethane⁵ directly before anchoring the test amine (4-methylpiperidine, **9**). For the preparation of spacer-modified, *p*-aminophenol-derived supports a different strategy was used. The sensitivity of ethers of *p*-aminophenol to light and oxygen made the preparation of the *para* analogues more difficult and inefficient. Therefore, the amines prepared by reduction of nitro alcohols **10** were protected in the form of triazenes **11** (Scheme 3). These triazenes, which served as masked diazonium ions, were very easily and effectively





Scheme 2.

attached to a Merrifield polymer⁷ (as indicated by the high-loading of diethylamine on 12; practically quantitative substitution of Cl by triazene⁸). Simple washing of the triazene gel 12 with a cold 10% TFA solution in dichloromethane regenerated the diazonium salt, which was ready to anchor a new amine. The overall exchange of amines was accomplished with barely detectible, within experimental error, lowering of loadings. The loadings of the test amine (4-methylpiperidine, 9) immobilized on the new polymers 12 (94 and 98% of the theoretical value) were significantly better than the loadings on the known supports^{5,6} without spacers 14 and 15 (64 and 69% of the theoretical value). In general the approach based on the direct preparation of triazenes on solid-phase gives polymers with lower loadings than the new strategy based on pre-loading of triazenes 11 prepared in solution and exchange of amines on solid-phase. In addition, the polymer bound triazenes 12 act as masked polymer-supported diazonium ions, have a good shelf life, and thus can be alternatives to the thermally stable polymer bound 4-chlorobenzenediazonium tetrafluoroborate (the so-called T2* linker).^{2c}

Polymer-supported reactions: In order to compare the performance of the classical linkers (the so-called *meta*-T2, *para*-T2) and the new supports (*meta*-C₃-T2, *meta*-C₆-T2, *para*-C₃-T2 and *para*-C₆-T2) two illustrative reactions on immobilized nortropinone were investigated (Scheme 4, Table 1). Anchoring of nortropinone (8-azabicyclo[3.2.1]octan-3-one) to the polymeric supports under previously found conditions gave polymers **16**. The Grignard addition of ethylmagnesium bromide showed the best performance on the *meta*-C₃ and *para*-C₃ supports giving 69 and 71% conversion of nortropinone

to adduct 17, as indicated by the ratio of product to substrate after cleavage of the linker with 10% TFA in dichloromethane. Under the same conditions, Grignard addition reactions on polymers with the meta-T2 and para-T2 linkers gave 53 and 56% conversion, respectively. Surprisingly the performance of the *meta*- C_6 and para-C₆ linkers was different (37 and 57% conversion, respectively). A complication of the aldol reaction of the triazene protected nortropinone is the formation of bisaldol 19.³ The supported aldol reaction also gave the best results on the polymer with the para-C₃ linker giving product 18 without bisaldol impurity 19, contrary to the other two supports where the amount of bisaldol 19 was significant (para-C₀ 20%, para-C₆ 33%). Analogous results were obtained for aldol reactions on the *meta* isomer. The observations indicate that the optimal linkers have the so-called C₃ spacer (1,3propanediol derived) regardless of the ring substitution pattern.

In summary, a new and efficient approach for preparation of resins with spacer bound diazonium ions that are masked (and thus stabilized) in the form of triazenes has been developed.⁹ The three carbon atom spacer modified linkers gave better yields and purities of products of aldol and Grignard reactions of immobilized nortropinone.

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Scheme 4.

Table 1. Conversion of the Grignard and the aldol reactions on different supports

Support 16	Loading ^a of nortropinone (mmol/g)	Conversion in Grignard reaction (%)	Conversion in aldol reaction (18:19, %) ^b
meta-C ₀	0.62	53	65:24
$meta-C_3$	0.57	69	76:12
$meta-C_6$	0.29	37	71:19
$para-C_0$	0.42	56	60:20
para-C ₃	0.52	71	77:<5
$para-C_6$	0.27	57	60:33

^a Loading determined from mass of nortropinone HCl obtained after cleavage with TFA and conversion of the TFA salt to the HCl salt.

^b Determined by ¹H NMR analysis of cleaved products.

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- 7. Procedure for the preparation of resin 12a and exchange of the triazene bound amine: Sodium hydride (0.88 g, 60%) suspension in oil, 22 mmol) was added to a stirred solution of 11a (5.522 g, 22 mmol) in dry THF (30 mL). After the hydride dissolved, Merrifield polymer (4 g, Novabiochem, 1% PS-DVB, 200-400 mesh, 1.1 mmol/g) was added and the mixture was heated at 55°C for 72 h with intermittent stirring. Then the polymer was washed repeatedly with water-MeOH, MeOH, DCM, water-DMF, DMF, DCM, MeOH, and was dried under a vacuum to give a light yellow powder (4.676 g, 0.89 mmol of Et₂NH/g, quantitative substitution). ¹³C NMR (CDCl₃): δ 156.9, 143.6, 121.3, 114.8, 66.9, 65.3, 46.0, 29.8, 13.0. The resin 12a (0.300 g) was swollen in DCM, cooled to 0°C and washed with a chilled 10% TFA in DCM (3 mL, 10 min), DCM, 10% TFA in DCM (3 mL, 10 min) and DCM (5×4 mL). Then the cold (-18°C) solution of 9 (10 equiv.) in DCM was added and the suspension was shaken and slowly warmed up to rt. After washing, the resulting gel was treated with 10% TFA in DCM and the cleaved amine was converted to the hydrochloride and dried to give pure **9**·HCl (0.034 g, 0.84 mmol/g).
- 8. Loading determined by microanalysis did not always accurately reflect the actual amount of amine bound to the polymer. Therefore, a better gravimetric method based on weighing the cleaved amine hydrochloride (weighing $Et_2NH\cdotHCl$ or 9·HCl) was used for comparing results.
- Structures of all new compounds were confirmed by spectrometric analyses and structures of polymers by gel-phase ¹³C NMR, IR and CHN analyses.