Pergamon

Tetrahedron Letters 43 (2002) 5305–5309

TETRAHEDRON LETTERS

A convenient 'catch, cyclize, and release' preparation of 3-thio-1,2,4-triazoles mediated by polymer-bound BEMP

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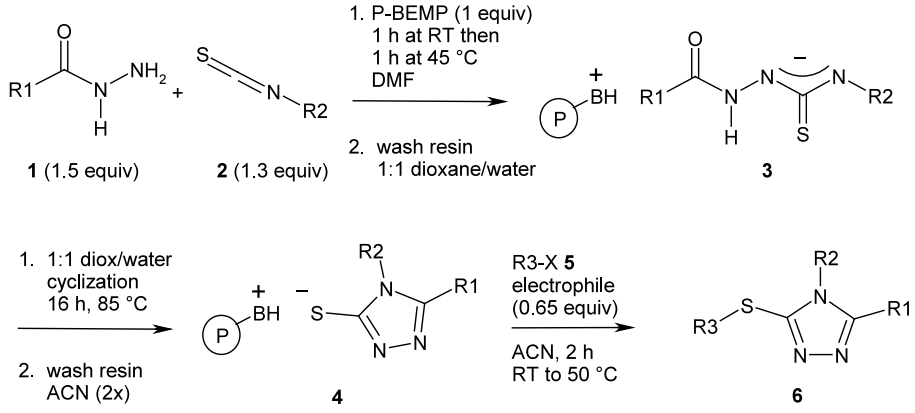
Received 27 March 2002; revised 29 May 2002; accepted 30 May 2002

Abstract—A robust 'catch, cyclize, and release' preparation of 3-thioalkyl-1,2,4-triazoles mediated by the polymer-bound base P-BEMP is described. This reengineered synthesis combines the chemical efficiency of the classical synthesis (three steps; three diversity points) with the practical benefits of resin-bound reagents (use of excess reagents to drive reactions to completion, no purification of intermediates, automation-friendly). Key advantages/limitations of this scheme, reagent compatibility, and the results of a representative 64-member combinatorial library are described and presented herein.

1. Introduction

An increasing number of resin-bound reagents are available to facilitate single-step and multi-step chemical transformations. Several reviews have now been written to describe the development, advantages, limitations, and applications of these solid-supported reagents.[1–4] With increasing frequency, medicinal chemists employ these new reagents to rapidly prepare drug-like hit identification libraries and to generate structure–activity relationships during property optimization.

We became interested in 3-thio-1,2,4-triazoles owing to the short classic synthesis (three steps; three-point diversity),[5,6] readily available pools of diversity reagents, and biological activity identified during in-house high-throughput screening efforts. As 3-thioalkyl 1,2,4-triazoles were under-represented in our corporate HTS collection, we sought a robust, easily automated, solution-phase preparation that not only reduced (or eliminated) the need for isolation of synthetic intermediates but was also complementary to reported solid-phase methods.[7]



Scheme 1. Preparation of 3-thio-1,2,4-triazoles.

Keywords: 1,2,4-triazole; 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine; parallel synthesis; solid-supported reagents.

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)01055-9

In this letter, we report a robust 'catch, cyclize, and release' preparation of 3-thioalkyl-1,2,4-triazoles mediated by the polymer-bound base, P-BEMP. Key advantages and limitations of this scheme, reagent compatibility, and the results of a representative 64-member array are described and presented herein.

2. Results and discussion

2.1. P-BEMP mediated synthesis

The reengineered synthesis described in Scheme 1 combines the chemical efficiency of the classical synthesis (three steps; three diversity points) with the practical benefits of resin-bound reagents (use of excess reagents, ease of use, automation-friendly). Central to this scheme is the highly basic, non-nucleophilic polymer-bound BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene, P-BEMP, Fig. 1).[8,9] Owing to these properties, P-BEMP is often the reagent of choice for deprotonation and *N*-alkylation of weakly acidic heterocycles.[10,11] In the 'catch, cyclize, and release' preparation outlined in Scheme 1, P-BEMP plays a key role in every step of the sequence.

In the 'catch' step, condensation of excess acyl hydrazide **1** and isothiocyanate **2** in DMF provides the diacylhydrazide that is then rapidly sequestered by the polymer-bound BEMP as ion-pair **3**. Owing to the resin-bound nature of **3**, the excess reagents/products (hydrazide **1**, isothiocyanate **2**, unsequestered diacylhydrazide) and high-boiling DMF are then easily removed during subsequent resin washing steps and replaced with 1:1 dioxane/water, a solvent found optimal for cyclization. While the cyclization rate of **3** to **4** is slower (~2–5 fold) than the classical solution-phase approach (NaOH, MeOH, 65°C), complete cyclization to the polymer-bound ion-pair 3-thio-1,2,4-triazole **4** is accomplished by heating at 85°C for 16 h.[12] If desired, the cyclization rate and reaction progress can be conveniently monitored by removal of several milligrams of resin from the reaction, treatment with dilute acetic acid (1% AcOH in ACN), and subsequent LCMS analysis of the released intermediates. As before, owing to the resin-bound nature of **4**, any non-acidic side-products produced during the cyclization are simply washed away from the resin as acetonitrile is introduced in preparation for the subsequent *S*-alkylation step (resin washed 2×, ACN). Treatment of ion pair **4** with an acetonitrile solution of alkylating agent **5** (rt, 1 h then 50°C, 1 h) 'releases' product **6** into the reaction solution. A substoichiometric amount of alkylating agent **5** minimizes the chance of product contamination as consumption of **5** is typically rapid and complete. Simple filtration, subsequent resin wash (2×), and solvent evaporation typically provides diverse 3-thioalkyl-1,2,4-triazoles **6** in excellent LCMS purity (>80%; estimated by ELSD)[13,14] and good overall yield (30–95% based on **5**). Further, the triazoles **6** are contaminated with very little halide (≪5% by elemental analysis) as the electrophile 'leaving group' (i.e. I, Br, Cl, tosylate) remains sequestered on P-BEMP. Typically, no further purification is needed.[15] A representative proton NMR spectrum of a typical crude product **7** is shown in Fig. 2. Additional characterization data and the generic synthetic protocol used to prepare **7** (and 1,2,4-triazoles described in Fig. 4) are provided in Ref. 16.

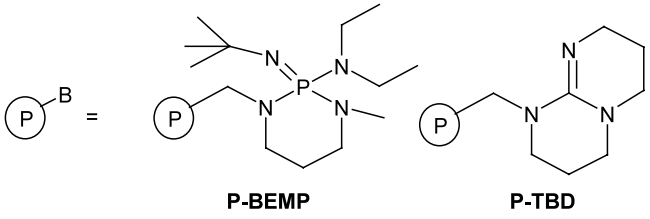


Figure 1. Structures of resin-bound bases.

2.2. Reagent compatibility

Parallel paneling experiments carried out during the library optimization phase quickly defined reagent applicability for this P-BEMP-mediated sequence. These experiments were typically configured in either Bohdan MiniBlocks (polypropylene tubes) or in trays of glass reaction vessels (Myriad CORE System)[17] to

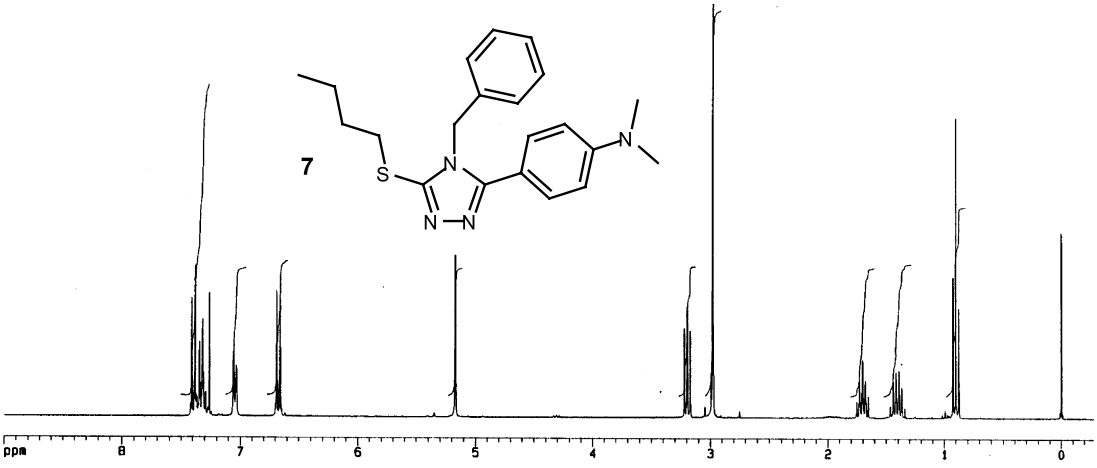


Figure 2. 400 MHz NMR of representative triazole **7** (crude).

test a single class of diversity reagent. For example, to identify suitable alkyl halides, ion-paired 3-thio-1,2,4-triazole **8** was treated in parallel with 0.05 M solutions of diverse alkyl halides **5** and then allowed to react under conditions projected for library synthesis. Additional details and representative results are provided in Fig. 3. Several observations are highlighted here.

2.2.1. Alkylating agents 5. Based on the paneling experiments described in Fig. 3, reagent compatibility can be summarized as follows. Unhindered alkyl iodides and bromides typically provide products with excellent purity and yield (**5b**,**c**), while unactivated alkyl chlorides (**5a**) frequently require more forcing conditions and subsequently result in products of lower purity/yield. Although more variable, excellent purity and acceptable product yields are obtained with many hindered 1° and 2° alkyl iodides and bromides (**5d**,**e**).[18] In general, many electron-poor and electron-rich, hindered and unhindered benzyl halides (**5g**,**h**), allyl halides (**5f**), and α-halo esters and amides (**5j**,**k**) are successfully employed. Aromatic halide substitution is frequently possible with activated systems (such as **5l**) but is very substrate dependent. Alkylating agents containing functional groups more acidic than the thiotriazole nucleus ($pK_a \sim 6.5$) are not tolerated when using the generic protocol.

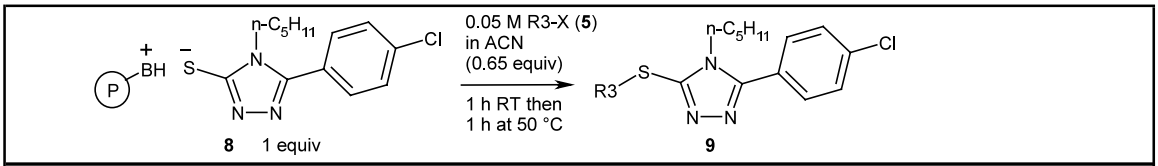
2.2.2. Acyl hydrazides 1. Related paneling experiments confirmed that many (un)branched alkyl (**1a**,**e**,**g**), substituted aryl (**1c**,**d**), heteroaryl (**1b**,**f**,**h**), and carboxamido (i.e. $R1 = CONH_2$) hydrazides are compatible with the sequence (refer to Fig. 4 for structures). Hydrazides may not contain functional groups that are more acidic than the thiotriazole nucleus ($pK_a \sim 6.5$), readily hydrolyzed (i.e. esters), or incompatible with strong nucleophiles. Hydrazides with severe steric hindrance (i.e. 1-naphthoic acid hydrazide) do not perform well.

2.2.3. Isothiocyanates 2. Similarly, experiments confirmed that many (un)branched alkyl isothiocyanates (**2a**,**e**,**h**), including those containing ethers (**2d**), olefins (**2b**) and a variety of saturated or aromatic heterocycles (**2c**,**f**,**g**), are compatible with the sequence. Isothiocyanates should not contain α-branching (thus R2 cannot be aryl or heteroaryl) as these analogs do not cyclize well (**3** to **4**) under these reaction conditions.

2.2.4. Resin-bound base. Preliminary studies indicated that individual reactions were faster and cleaner with P-BEMP (Fluka cat. # 20026, 2.2 mmol/g) than with a resin-bound guanidine base (P-TBD, Fluka cat. # 90603). This is presumably due to P-BEMPs increased basicity, lower nucleophilicity, and better dispersion properties especially in these polar solvents.[8,9]

2.3. Applications

Using this reagent compatibility information, more than 2500 diverse, yet drug-like,[19] triazoles were prepared for hit identification purposes. The 64 compounds highlighted in Fig. 4 are a representative subset of a larger hit identification array. With little or no protocol modification, this robust 'catch, cyclize, and release' strategy was used successfully on a number of manual and automated synthesis platforms (Myriad CORE System, Bohdan MiniBlock, Argonaut Quest 210). More recently, this convenient solution-phase method was applied to a number of hit optimization



Electrophile (**5**)	Product (**9**)	% Purity[a]	% Yield[b]	Electrophile (**5**)	Product (**9**)	% Purity[a]	% Yield[b]
5a	**9a**	79	71 (22)	**5g**	**9g**	100	97 (57)
5b	**9b**	100	81 (45)	**5h**	**9h**	96	65 (33)
5c	**9c**	100	93 (61)	**5i**	**9i**	52	58 (26)
5d	**9d**	87	95 (44)	**5j**	**9j**	100	91 (56)
5e	**9e**	100	92 (58)	**5k**	**9k**	100	77 (40)
5f	**9f**	87	67 (27)	**5l**	**9l**	100	70 (39)

[a]identity and purity determined by LCMS using ELS detection (see reference 13)
[b]crude product yield (purified yield after prep. HPLC)

Figure 3. Representative results of paneling experiment—alkylating agents **5**.

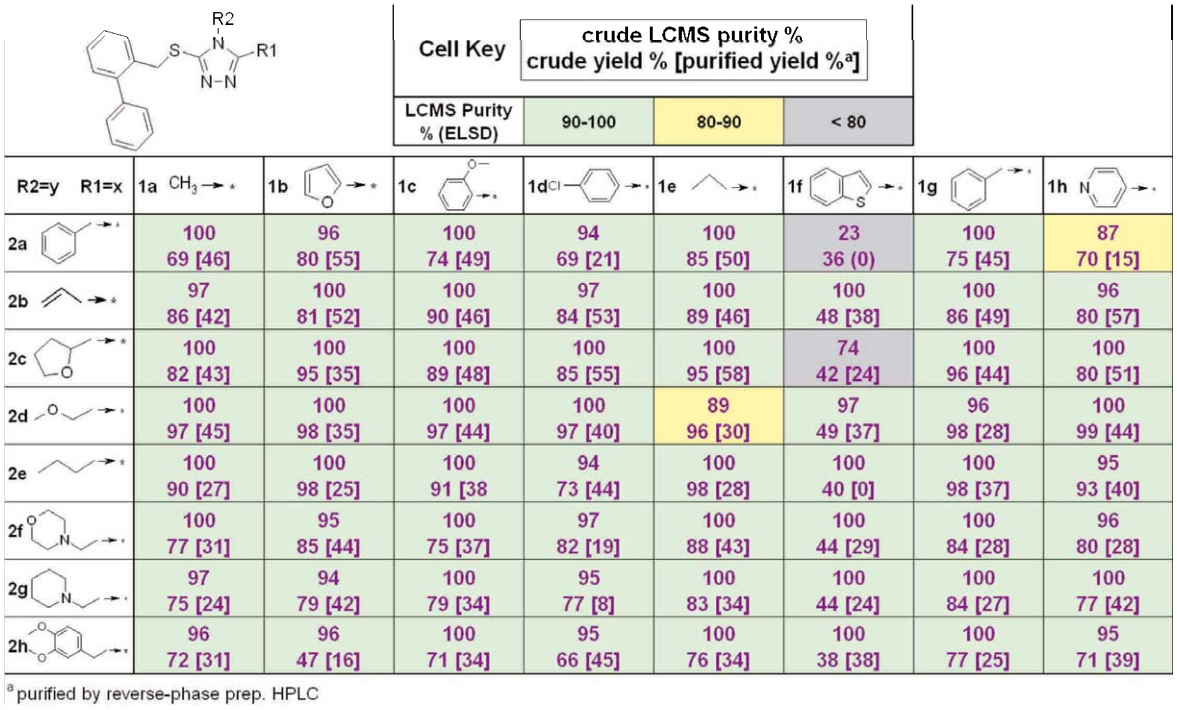


Figure 4. Results for representative subset of hit identification array.

efforts. These efforts will be the subject of future communications.

3. Conclusion

In this letter, we report a robust 'catch, cyclize, and release' preparation of 3-thioalkyl-1,2,4-triazoles mediated by the polymer-bound base, P-BEMP. The reengineered synthesis marries the chemical efficiency of the classical synthesis (three steps; three diversity points) with the practical benefits of resin-bound reagents (excess reagents, ease of use, automation-friendly). We believe this is the first reported solution-phase synthesis of 3-thioalkyl-1,2,4-triazoles that benefits from the use of excess reagents to drive reactions to completion, yet does not require purification of either synthetic intermediates or final products.[20] Efforts to extend this 'catch, cyclize, and release' strategy to other heterocyclic families are on-going and will be the topic of future reports.

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12. Typically, cyclizations are complete in <8 h. However, the 16 h reaction time was selected to maximize the cyclization for any particularly problematic combinations during parallel synthesis.
13. Purity for all compounds was determined by a C18 reverse phase HPLC column, Keystone Aquasil (1×40 mm) in 10–90% ACN/H_2O containing 0.02% TFA (3.6 min gradient) and monitored at 214 nm using a UV detector and by a SEDEX 75 evaporative light scattering detector (ELSD) operating at 42°C. Purity scores reported herein are based on ELSD. LCMS M+H signals were consistent with expected MW for all reported products.
14. It was recognised during the optimization phase of this effort that LCMS purity analysis by ELSD (evaporative light scattering detection) consistently provided a more accurate estimate of product purity (NMR used as benchmark) than did UV-based detection (214 nm).

15. When the purified yield data for this manuscript was collected in our laboratory (2000), it was customary to experience a significant loss in yield (~50%) owing to cumulative losses during purification and the post-synthesis processing (transfers, fractionation, fraction combination etc.). Further, premature precipitation of these highly pure 'crude' products (from concentrated DMSO solutions prior to fractionation) was in some cases problematic and led to greater losses.
16. Synthetic protocol for triazole **7** and representative 64-member array: Polymer-bound BEMP (60 mg, 0.126 mmol, 1 equiv.) was added to a fritted reaction vessel, swelled with DMF (3×) then excess solvent was aspirated to waste. DMF solutions of 4-dimethylaminobenzhydrazide **1** (0.5 M, 0.380 mL, 0.189 mmol, 1.5 equiv.) and benzyl isothiocyanate **2** (0.5 M, 0.330 mL, 0.164 mmol, 1.3 equiv.) were added to the vessel. The reaction vessel was vortexed for 1 h at room temperature and then 2 h at 45°C. Excess solution was then aspirated to waste. The resin was washed with 2-mL portions of DMF (3×) then 1:1 dioxane/H_2O (2×). A 1:1 mixture of dioxane/H_2O (3 mL) was then added to the reaction vessel containing resin-sequestered diacylhydrazide **3**. The resin was then mixed and heated at 85°C for 16 h to provide **4**. After cooling, the resin was successively washed with 2-mL portions of 1:1 dioxane/H_2O (3×) and acetonitrile (2×). A solution of butyl iodide **5** (0.02 M, 2 mL, 0.082 mmol, 0.65 equiv.) in acetonitrile was then added to the resin and the vessel was mixed for 2 h at room temperature followed by 1 h at 50°C. After cooling, the solution containing triazole **7** was drained into a tared tube. The resin was then washed twice with acetonitrile (2 mL). All filtrates were collected in the tube. Evaporation of solvents provided triazole **7** as a clear glass (29 mg, 96% yield based on alkyl halide). LC/MS [M+H]=367.0; 100% purity (ELS detector). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, J=8.9 Hz, 2*H*), 7.35 (m, 3*H*), 7.08 (d, J=6.7 Hz, 2*H*), 6.70 (d, J=8.9 Hz, 2*H*), 5.20 (s, 2*H*), 3.23 (t, J=7.4 Hz, 2*H*), 3.01 (s, 6*H*), 1.73 (m, 2*H*), 1.43 (m, 2*H*), 0.93 (t, J=7.3 Hz, 3*H*). Elemental analysis (I), 1.2%.
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18. BEMP is frequently used to effect dehydrohalogenation owing to its strongly basic and non-nucleophilic character. However, dehydrohalogenation is minimized under these conditions as the resin-bound base is in its conjugate acid form **4**.
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20. Since submission of this work, Theoclitou et al. (J. Comb. Chem., web release date 04-04-2002) has reported a parallel solution-phase method for the preparation of 3-thio-1,2,4-triazoles. In contrast to our work, HPLC purification was required to separate the desired product from reaction byproducts and excess reagents.