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A convenient 'catch and release' synthesis of fused 2-alkylthio-pyrimidinones mediated by polymer-bound BEMP

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Abstract—A robust 'catch and release' synthesis of fused 2-alkylthio-3-substituted-pyrimidinones mediated by the polymer-bound base P-BEMP is described. This reengineered synthesis combines the efficiency of the classical synthesis (three steps, three diversity points) with the practical benefits of resin-bound reagents. The solution-phase strategy, reagent compatibility, and the results of a representative 48-member combinatorial library are described and presented herein.

1. Introduction

We recently reported a multi-step 'catch and release' synthesis of 3-alkylthio-1,2,4-triazoles mediated by the polymer-bound base P-BEMP.[1] This triazole synthesis exploits both the efficiency of the classical synthesis (three synthetic steps; three diversity points) and the practical benefits of resin-bound reagents (use of excess reagents, ease of use, automation-friendly).[2–5] It quickly became evident this simple 'catch and release' strategy could be further exploited for synthesis of other heterocycles. Fused pyrimidin-4-ones **9** were considered attractive targets owing to the short concise synthesis (three steps; three-point diversity),[6,7] readily available pools of diversity reagents,[8] and diverse reported biological activity.[9–11] As fused pyrimidin-4-ones were poorly represented in our corporate compound collection, we sought a robust solution-phase approach that not only eliminated the need for isolation of synthetic intermediates but was also complementary to a reported solid-phase method.[12] In this letter, we report a 'catch and release' synthesis of 2-alkylthio-3-substituted-3*H*-quinazolin-4-ones and thienopyrimidin-4-ones mediated by the polymer-bound base, P-BEMP. Application highlights, reagent compatibility, and the results of a representative 48-member array are described herein.

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

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2. Results and discussion

2.1. P-BEMP enabled synthesis

The 'catch and release' sequence is described in Scheme 1. Central to this scheme is the strongly basic, nonnucleophilic polymer-bound BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene, P-BEMP, Fig. 1).[13,14] Owing to these properties, P-BEMP is often the reagent of choice for deprotonation and *N*-alkylation of weakly acidic heterocycles.[15,16] In this 'catch and release' preparation, P-BEMP plays a key role in nearly every step of the sequence.

2.2. The 'catch' step

A solution of substituted anthranilic acid ester **1** (1.3 equiv.) and isothiocyanate **2** (1.5–2.0 equiv.) in dimethylsulfoxide (DMSO) is heated at 100°C for three days to effect both addition and subsequent cyclization to the 2-thioxo-quinazolin-4-one **3**. Polymer-bound P-BEMP (1 equiv.) and DMF[17] are then added to cleanly sequester the acidic heterocycle as ion-pair **4**. Owing to the polymer-bound nature of ion-pair **4**, the excess reagents/products (anthranilic ester, isothiocyanate, and 2-thioxo-quinazolinone **3**) are easily removed during subsequent resin washing steps. Surprisingly, DMSO is an optimal and convenient solvent for preparation of intermediates **3**, **6** and the subsequent conversion to ion-pair **4**.[18,19] Under these conditions, reaction of isothiocyanate **2** with anthranilic ester **1** is believed to

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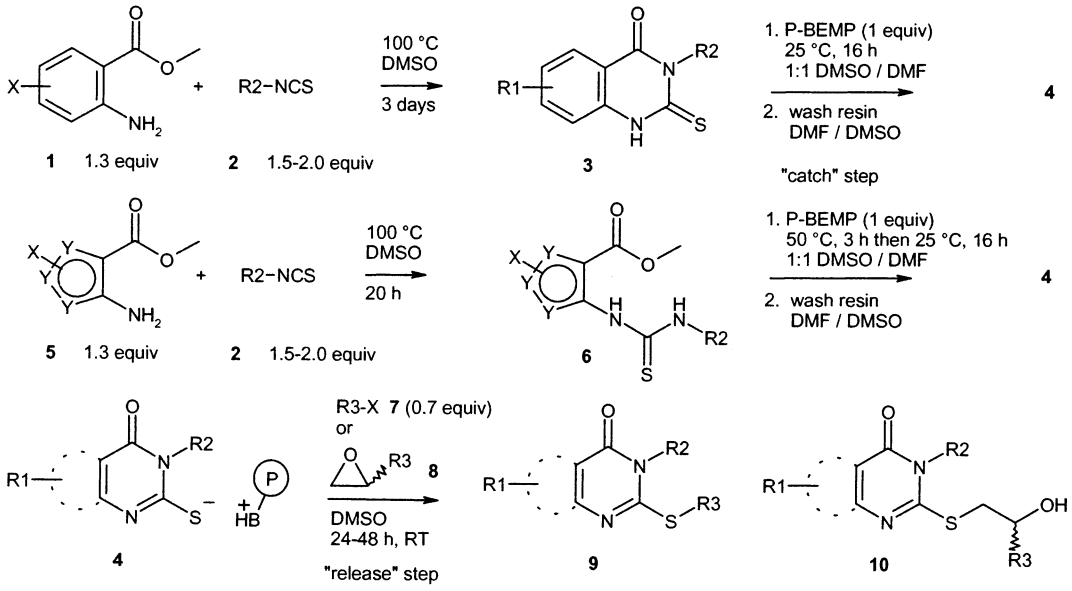


Scheme 1. 'Catch and release' synthesis of fused 2-alkylthio-pyrimidinones **9**, **10**.

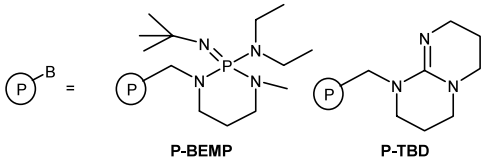


Figure 1. Structure of polymer-bound BEMP.

be the rate limiting step of the transformation as the expected thiourea intermediate (analogous to **6**) is not observed by analytical methods (LCMS, NMR).

Based on the above observations, we were subsequently surprised to find primarily accumulation of uncyclized thiourea **6** when *thiophene-based* aminoesters **5** and isothiocyanates **2** are reacted as described above (Scheme 1). The results of additional experiments indicate that (1) consumption of **5** (formation of **6**) is, in most cases, complete after heating for 20 h at 100°C; (2) heating for longer than 20 h is typically counterproductive as thioureas **6** tend to slowly degrade rather than cyclize; (3) addition of P-BEMP (1 equiv.) to a solution of thiourea **6** rapidly effects both sequestration and cyclization to ion-pair **4**; and (4) excess reagents and by-products are conveniently removed from ion-pair **4** by a simple wash of the resin. The preferred protocol for preparation of ion-pair **4** from thiophene-based aminoesters **5** is highlighted in Scheme 1.

2.3. The 'release' step

DMSO is also an advantageous solvent for the 'release' step.[20] As a result, it is convenient and robust to couple the 'release' step with a subsequent high throughput HPLC purification step for preparation of large arrays. Room temperature treatment of ion-pair **4** with a DMSO solution of alkylating agent (i.e. **7a**–**d**) or mono-substituted epoxide (i.e. **8a**–**d**) 'releases' thioethers **9** or **10** into the solution. Simple filtration and subsequent resin wash typically provides DMSO solutions of crude products **9** or **10** in moderate to excellent purity (LCMS-UV214; 50–100%).[21,22] A substoichiometric amount of electrophile **7** or **8** minimizes product contamination as consumption of electrophile is typically complete in 2–8 h. The scale of the experiment is configured such that the resulting volume of DMSO solution (containing products **9** or **10**) is compatible with the injection volume of the reverse-phase HPLC purification step.[23] While we find it convenient to use DMSO in the release step during array production, similar (though more variable) results were obtained using acetonitrile (ACN) during building block qualification experiments (refer to Fig. 3 and discussion below). For example, a proton NMR spectrum of representative crude quinazolinone **12a** ('released' by treatment of **11** with 1-bromopentane **7a** in ACN) is shown in Figure 2. Generic synthetic protocols for array production (see representative fused pyrimidin-4-ones in Fig. 4) and quinazolinone **12a** are provided in Ref. 25.[24]

2.4. Reagent compatibility

Building block qualification experiments were used to define reagent compatibility for this P-BEMP-mediated sequence. These experiments (designed to test the compatibility of a single class of diversity reagent) were typically configured for either the Robbins FlexChem™ or Argonaut Quest210™ platforms.[26] For example, to identify suitable electrophiles, ion-paired quinazolin-4-one **11** was treated in parallel with 0.1 M solutions of diverse alkyl halides (i.e. **7a**–**d**) or epoxides (i.e. **8a**–**d**) then allowed to react under conditions projected for library synthesis. Additional details and representative results are provided in Figure 3. Several observations are highlighted here.

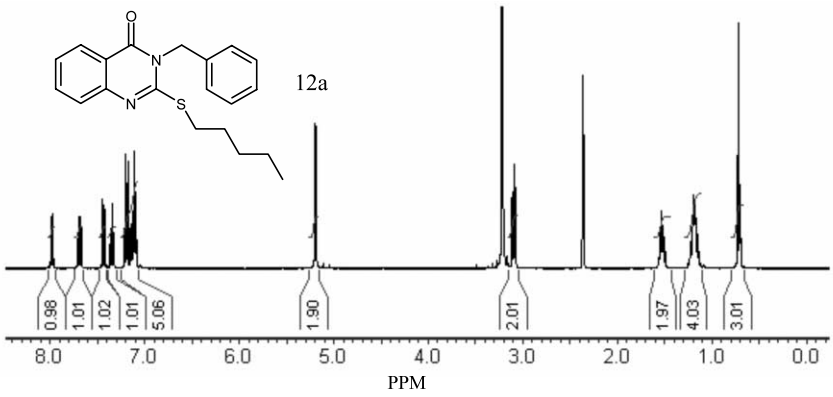
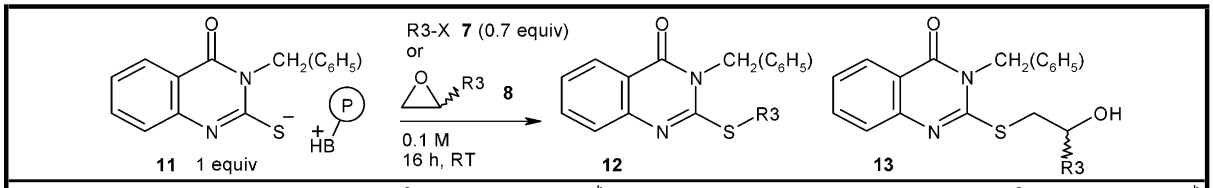
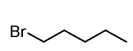
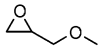
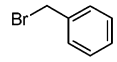
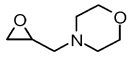
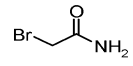
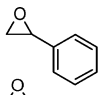
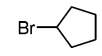


Figure 2. 400 MHz NMR of representative quinazolinone **12a** (crude).



Electrophile (**7**)	Product (**12**)	% Purity[a]	Solvent	% Yield[b]	Electrophile (**8**)	Product (**13**)	% Purity[a]	Solvent	% Yield[b]
7a 	**12a**	100	ACN	76 (97)	**8a** 	**13a**	63	DMSO	37
7b 	**12b**	90	ACN	75 (98)	**8b** 	**13b**	77	DMSO	31
7c 	**12c**	78	ACN	32 (46)	**8c** 	**13c**	52	DMSO	38
7d 	**12d**	91	ACN	60 (92)	**8d** 	**13d**	79	DMSO	31

[a]identity and purity determined by LCMS using UV214nm detection
[b]purified yield after preparative HPLC (crude yield in parentheses). Yield based on electrophile **7**,**8**.

Figure 3. Representative results from qualification experiments—electrophiles **7**, **8**.

Reagents containing functional groups more acidic than the fused 2-thioxopyrimidinone nucleus ($pK_a \sim 8.5$)[27] are not tolerated when using this protocol.

2.4.1. Electrophiles 7, 8. Based on experiments described in Figure 3, compatibility trends for alkylating agents parallel those reported earlier for 3-thio-1,2,4-triazoles.[1,12] Most common alkyl iodides and bromides are compatible whether hindered or not (**7a**,**d**). In addition, many diverse benzyl halides (**7b**), α-haloesters, and amides (**7c**) are successfully employed. For mono-substituted epoxides such as **8a**–**d**, regiospecific ring opening (S_N2 attack at least hindered position) provides the corresponding 2° alcohol derivatives **13a**–**d**. As exemplified in Figure 3, use of epoxides as electrophile input typically provides crude products of lower purity and yield compared to those derived from alkyl halides

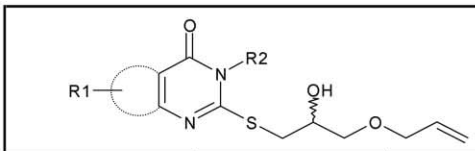
2.4.2. Aminoesters 1, 5. Many readily-accessible[8] phenyl- and thienyl-based aminoesters (i.e. **1a**–**c**, **5a-c**, see Fig. 4) are compatible. Aminoesters containing neutral or electron-donating groups (i.e. alkoxy, alkyl, H) at open ring positions performed best. In contrast, ring substitution with electron-deficient groups (i.e. Cl, F) rapidly decrease performance of these inputs under these general conditions. Generally, the yields of products (**9**, **10**) derived from anthranilic esters **1** are superior to those derived from thienyl-based aminoesters **5**.

2.4.3. Isothiocyanates 2. With a few exceptions, compatibility trends for isothiocyanates **2** parallel those reported earlier for 3-thio-1,2,4-triazoles.[1] Many (un)branched alkyl (i.e. **2a**,**b**,**c**,**e**) and substituted benzyl isothiocyanates (i.e. **2d**,**f**) are compatible with the sequence (Fig. 4). Aryl isothiocyanates (i.e. **2g**,**h**) are also compatible but acylisothiocyanates (R-CO-NCS) are not.

2.4.4. Resin-bound base. P-BEMP (Fluka cat. # 20026, 2.2 mmol/gram) was the only polymer-bound base investigated during this work.[28]

2.5. Application

Using this reagent compatibility information and these generic protocols, more than 3000 diverse, yet drug-



Cell Key crude LCMS purity % (purified yield %[a])

LCMS Purity %	80-100	50-80	< 50

aminoester \ R2-NCS	1a	1b	1c	5a	5b	5c
2a	No Data	88 (51)	80 (30)	87 (13)	66 (38)	95 (5)
2b	80 (21)	100 (24)	72 (22)	91 (17)	81 (30)	96 (8)
2c	63 (40)	81 (63)	80 (35)	100 (27)	77 (43)	100 (13)
2d	68 (34)	84 (45)	70 (15)	97 (13)	92 (21)	48 (2)
2e	65 (47)	88 (76)	77 (27)	100 (31)	76 (32)	95 (5)
2f	62 (30)	14 (2.4)	76 (57)	97 (17)	90 (22)	96 (9)
2g	84 (50)	100 (72)	89 (45)	92 (18)	67 (3)	100 (11)
2h	67 (28)	91 (44)	80 (35)	75 (10)	83 (9)	54 (5)

[a] purified by reverse-phase preparative HPLC

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

like,[29] fused 2-alkylthio-3-substituted-pyrimidin-4-ones (**9**, **10**) were prepared for hit identification purposes (90% registration rate after purification) using the Robbins FlexChem™ platform. The 48 compounds highlighted in Figure 4 are a representative subset of this hit identification array.[30] This subset illustrates the trends mentioned earlier in this report. With little modification, this robust 'catch and release' strategy should be amenable to other parallel synthesis platforms as well.

3. Conclusion

In this letter, we report a robust 'catch and release' preparation of 2-alkylthio-3-substituted-3*H*-quinazolin-4-ones and thienopyrimidin-4-ones mediated by the polymer-bound base, P-BEMP. This convenient synthesis combines the efficiency of the classical synthesis (three steps; three diversity points) with the practical benefits of resin-bound reagents. We believe this is the first reported solution-phase parallel synthesis of these heterocycles. Efforts to extend this 'catch and release' paradigm to other heterocycles are in progress and will be the topic of future reports.

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17. Addition of DMF enhances resin swelling and creates a free-flowing suspension.
18. To our knowledge, DMSO has never been reported as a preferred solvent for quinazolinone ring formation.
19. Advantages include clean and reliable conversion, excellent solubility of reagents and intermediates, minimal evaporative solvent loss during long periods of heating, and compatibility with the 'release' and purification steps.
20. In our previous work with P-BEMP sequestered 3-thio-1,2,4-triazoles, ACN was an optimal solvent when employing alkyl halides and ethanol was optimal for nucleophilic epoxide ring opening. To our surprise, use of ACN for preparation of **9** frequently is problematic owing to poor product solubility in ACN. Further, epoxide ring opening in ethanol provides products **10** with low purity (<40%). In contrast, *S*-alkylation of ion-pair **4** in DMSO is reliable with both alkyl halides and epoxides. While use of DMSO in the 'release' step (for both epoxides and alkylating agents) does require introduction of a purification step, a single, robust, production protocol (with fewer product solubility issues and high success rates) is very convenient.
21. Although not emphasized in this report, the corresponding 2-thioxo-2,3-dihydro-1*H*-quinazolin-4-ones **3** are also obtained in excellent purity (70–100%) after treatment of **4** with dilute AcOH/ACN solution.
22. Purity data reported here 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. LCMS M+H signals were consistent with expected MW for all reported products.
23. Purification was carried out using a semipreparative YMC Combiprep ODS-A reversed-phase column (20 mm×50 mm, particle size S-5 μm, 750 μL injection volume) via use of a 10–95% gradient of water/acetonitrile (4 min gradient, 25 mL/min flow rate) on a Gilson HPLC system.
24. The generic protocols reported here were developed to maximize scope and product diversity. In cases where specific individual compounds (or a more narrow scope) are desired, significantly improved purity and yield are typically achieved by straightforward tuning of the sequence (variation of temperature/time).
25. Synthetic protocols for quinazolinone **12a** and representative 48-member array:
*Formation of **4** from anthranilic acid esters **1***: DMSO solutions of anthranilic ester **1** (0.3 M, 0.43 mL, 0.13 mmol, 1.3 equiv.) and isothiocyanate **2** (0.4 M, 0.38 mL, 0.15 mmol, 1.5 equiv.) were mixed and heated at 100°C for three days. DMF (1 mL) and P-BEMP (45 mg, 0.1 mmol, 1 equiv.) were added to each reaction then mixed at room temperature overnight.
*Formation of **4** from aminoesters **5***: DMSO solutions of aminoester **5** (0.5 M, 0.4 mL, 0.195 mmol, 1.3 equiv.) and isothiocyanate **2** (0.7 M, 0.32 mL, 0.23 mmol, 1.5 equiv.) were mixed and heated at 100°C for 16 h. DMF (1 mL) and P-BEMP (68 mg, 0.15 mmol, 1 equiv.) were added to each reaction well and mixed at 50°C for 3 h then at room temperature overnight.
'Release step' used in array production: Excess solution was aspirated to waste. The resin was washed with 1 mL portions of DMF (3×) then DMSO (1×). A solution of alkylating agent or epoxide (0.14 M, 0.5 mL, 0.07 mmol, 0.7 equiv.) in DMSO was then added to resin **4**. The suspension was then mixed for 24–48 h at room temperature. The solution containing fused pyrimidinone **9** or **10** was drained directly into a deepwell 96-well microtiter plate. The resin was subsequently washed with a 0.2 mL portion of DMSO. The wash volume was also drained directly into the deepwell 96-well microtiter plate. DMSO solutions from this plate (0.7 mL per well) were injected directly into the preparative HPLC.
*'Release' step for preparation of **12a***: Excess solution was aspirated to waste. The resin was washed with 1 mL portions of DMF (3×) then ACN (2×). A solution of 1-bromopentane **7a** (0.07 M, 1 mL, 0.07 mmol, 0.7 equiv.) in acetonitrile was then added to the resin and the suspension was mixed for 16 h at room temperature. The solution containing quinazolinone **12a** was drained into a tared tube. The resin was then washed with 1 mL portions of warm acetonitrile (5×). All filtrates were collected in the tube. Evaporation of ACN provided quinazolinone **12a** as a clear glass (24 mg, 97% yield based on alkyl halide). LC/MS [M+H]=339.0; 100% purity (UV214 nm). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 7.97 (d, J=8.1 Hz, 1*H*), 7.68 (t, J=7.7 Hz, 1*H*), 7.43 (d, J=8.1 Hz, 1*H*), 7.34 (t, J=7.5 Hz, 1*H*), 7.15 (m, 5*H*), 5.19 (s, 2*H*), 3.10 (t, J=7.3 Hz, 2*H*), 1.54 (m, 2*H*), 1.19 (m, 4*H*), 0.72 (t, J=7.1 Hz, 3*H*).
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28. In our triazole work, the performance of P-BEMP was superior (faster/cleaner reactions) to a resin-bound guanidine base (P-TBD, Fluka cat. #90603). This is presumably due to P-BEMP's increased basicity, lower nucleophilicity, and better dispersion properties especially in these polar solvents.
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30. When the purified yield data for this manuscript was collected in our laboratory, it was customary to experience a significant loss (~50%) owing to cumulative losses during purification and the post-synthesis processing (transfers, fractionation, fraction combination etc.). Further, additional yield loss was expected here as the maximum injection volume allowed by the HPLC purification system (0.75 mL) limited the volume of DMSO used to wash resin after product release.