Fluorous-Phase Synthesis

A Fluorous-Phase Pummerer Cyclative-Capture Strategy for the Synthesis of Nitrogen Heterocycles**

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Nitrogen-containing heterocyclic organic compounds in the form of biologically active drugs or agents play an important role in the pharmaceutical and agrochemical industries.[1] The development of new strategies for the assembly of collections of heterocyclic compounds in a rapid and efficient high-throughput manner is therefore a key activity in synthetic chemistry.[2]

The Pummerer reaction[3] provides a useful tool for the synthesis of heterocyclic compounds.[4] We recently reported a solid-phase approach to oxindoles that utilizes the Pummerer cyclization of substrates attached to a resin by an "enabling" sulfur atom.[5] The approach is limited by the synthetic sequence required to access the immobilized heterocyclic framework (immobilization–oxidation–cyclization). A more general limitation, common to many solid-phase processes, arises from the considerable investment required to optimize solid-phase sequences because of difficulties in monitoring transformations.[6] Herein, we report our success in addressing these issues and describe a fluorous-phase[7,2b] Pummerer cyclative-capture strategy for the synthesis of a range of N heterocycles.

Our approach is based on the addition of thiols to glyoxamides **1** to form hemithioacetals at the correct oxidation level for activation and Pummerer cyclization. This constitutes a new, general strategy for triggering Pummerer cyclizations.[8] The use of a thiol-containing phase tag[9,10] leads to cyclative capture of the substrate. The choice of a fluorous phase tag both allows reactions to be monitored conveniently and allows phase-tag-assisted purification at each stage of the process. Our approach constitutes the first

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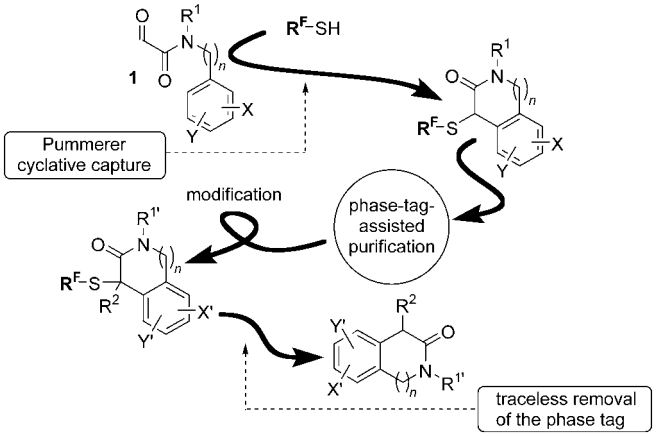
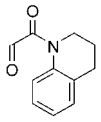
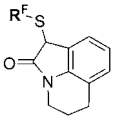
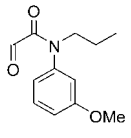
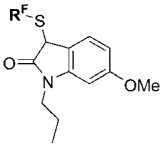
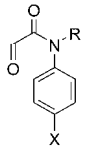
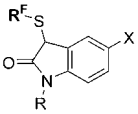
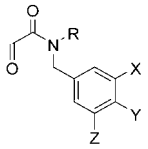
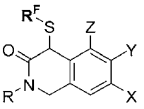
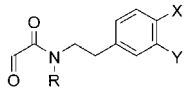
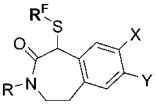
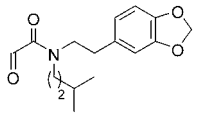
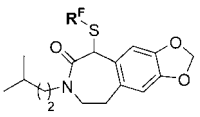
example of fluorous-phase cyclative capture and utilizes a fluorous-phase scavenging reagent in a novel manner. Upon completion of the sequence, the fluorous phase tag can be removed under mild electron-transfer conditions[11] (Scheme 1). The treatment of readily accessible glyoxamide[12] starting materials with $C_8F_{17}CH_2CH_2SH$ results in rapid capture of the substrate and hemithioacetal formation. In the same reaction pot, activation with trifluoroacetic anhydride and treatment with $BF_3{\cdot}OEt_2$ then gave the product heterocycle in good yield after rapid purification by fluorous solid-phase extraction (FSPE).[7] The fluorous-phase Pummerer cyclative capture of a range of glyoxamides is summarized in Table 1.



Scheme 1. Fluorous-phase Pummerer cyclative-capture strategy ($\mathbf{R^F}$ = fluorous alkyl).

Table 1: Fluorous-phase Pummerer cyclative capture of glyoxamides.[a]

Entry	Glyoxamide	Tagged heterocycle[b]	Yield [%][c]
1			65
2			75[d]
3	X = Cl, R = Me			79
4	X = Br, R = *n*Pr			85
5	X = F, R = Me			80
6	X,Y,Z = H, R = Me			45
7	X = OMe, Y,Z = H, R = *n*Pr			51[e]
8	X,Y,Z = OMe, R = *n*-pentyl			60
9	X = H, Y = OMe, R = *n*Pr			76[f]
10	X = Y = OMe, R = *n*-pentyl			98
11			82

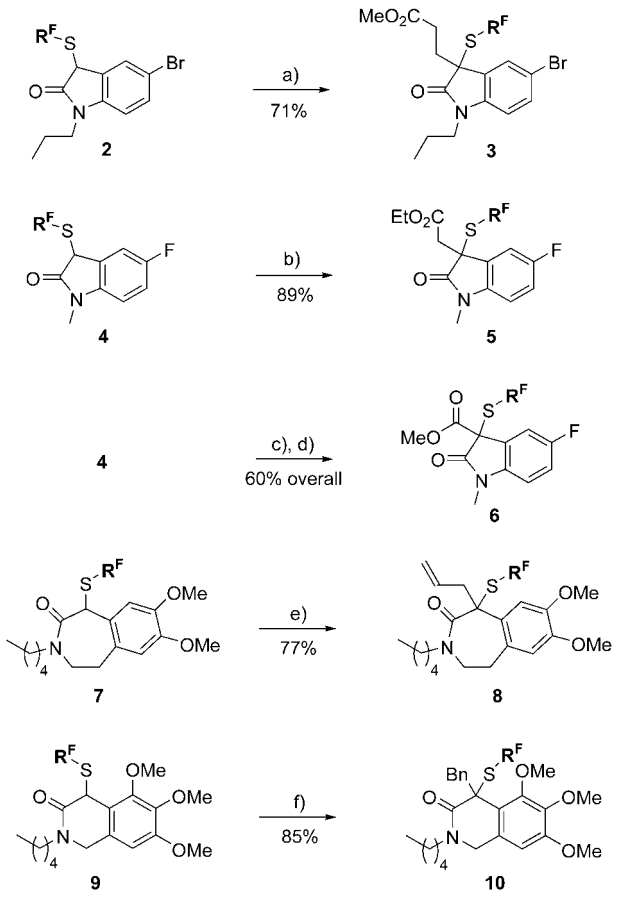
[a] Conditions: $C_8F_{17}CH_2CH_2SH$, CH_2Cl_2, 18 h, then trifluoroacetic anhydride, 1 h, then $BF_3{\cdot}OEt_2$, 1 h; see Supporting Information for details. [b] $\mathbf{R^F} = C_8F_{17}CH_2CH_2$. [c] Yield of isolated product. [d] Isomer ratio: 5:1. [e] Isomer ratio: ~1:1. [f] Isomer ratio: ~2:1. Major isomers shown.

Oxindoles (Table 1, entries 1–5), tetrahydroisoquinolinones (Table 1, entries 6–8), and tetrahydrobenzazepinones (Table 1, entries 9–11) can be prepared by straightforward variation of the glyoxamide substrate. For the formation of six- and seven-membered heterocycles (Table 1, entries 6–11), electronic activation of the aromatic ring leads to higher yields of the product. In contrast, the formation of oxindoles (Table 1, entries 1–5) proceeds efficiently with neutral, electron-deficient, and electron-rich substrates.

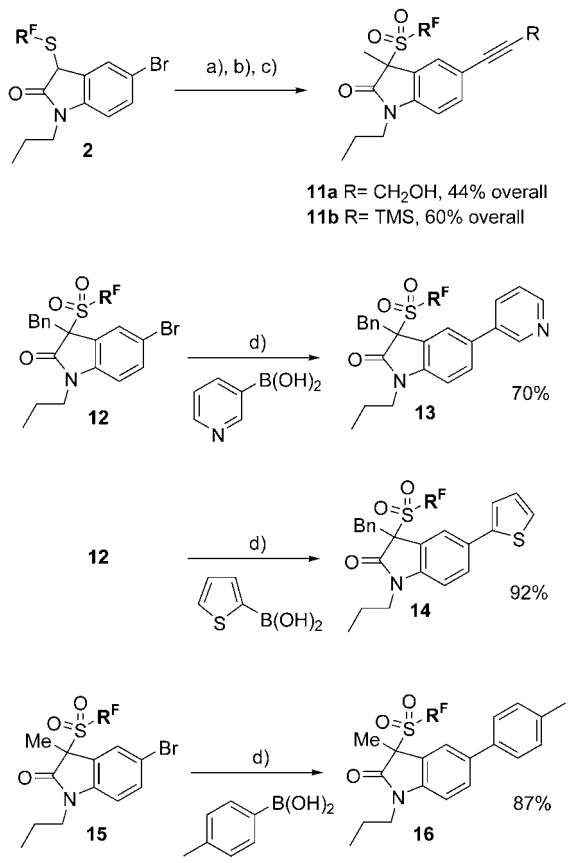
The Pummerer cyclative-capture process allows convenient access to fluorous-tagged heterocyclic frameworks. These tagged heterocycles can be modified in a variety of ways. The sulfur-atom linkage to the fluorous phase tag can be used to facilitate elaboration by alkylation and acylation reactions (Scheme 2). For example, adducts **3** and **5** were prepared by Michael addition and alkylation, respectively, whereas the fluorous tetrahydrobenzazepinone and tetrahydroisoquinolinone derivatives **7** and **9** were alkylated in an analogous fashion. Ester **6** was prepared by O acylation followed by DMAP-catalyzed rearrangement.[13] Crucially, excess reagents can be used to drive reactions to completion, as purification after each modification step can be carried out conveniently by FSPE.

The transformations illustrated in Scheme 3 show the compatibility of the linker system with Pd-catalyzed cross-coupling technologies. Oxidation of the linking sulfur atom to the corresponding sulfone further facilitates elaboration of the tagged heterocyclic scaffolds. For example, sequences to prepare alkynes **11a** and **11b** include sulfone-assisted alkylation and Sonogashira cross-coupling. Tagged 5-bromooxindoles **12** and **15** readily undergo Suzuki cross-coupling with aryl and heteroaryl boronic acids to give **13**, **14**, and **16**. Again, purification after each modification step can be conveniently carried out by FSPE.

Traceless cleavage of the fluorous tag is possible with a range of electron-transfer reagents;[14] however, we have found that reduction with SmI_2[5,11a] results in the clean release of the heterocyclic product from the fluorous phase. No additives are required to activate SmI_2,[15] regardless of the oxidation state of the sulfur atom, because of the activated nature of the carbon–sulfur linkage to the phase tag. For the cleavage of fluorous sulfides, FSPE can again be used to assist



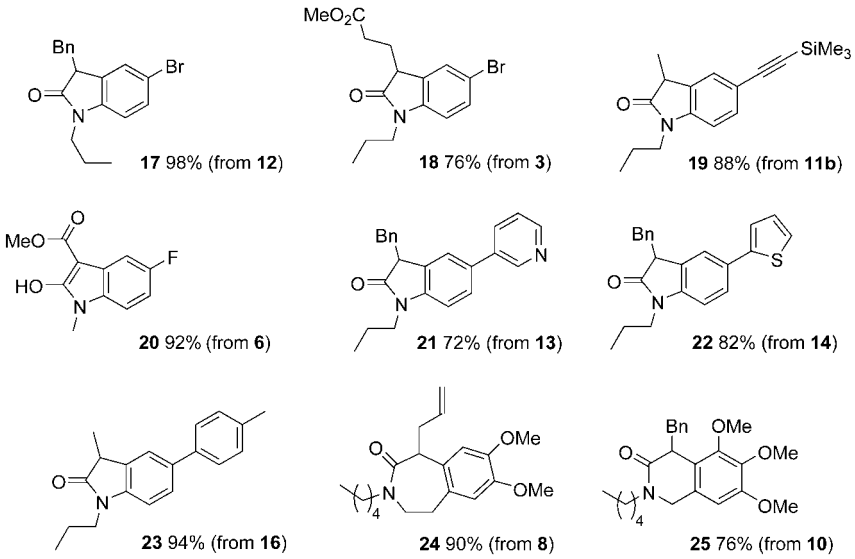
Scheme 2. Manipulation of fluorous-tagged heterocycles—modifications α to sulfur ($\mathbf{R^F} = C_8F_{17}CH_2CH_2$). Reagents and conditions: a) NaOMe, MeOH, methyl acrylate, 18 h; b) LDA, THF, −78 °C, 2.5 h, ethyl bromoacetate; c) methyl chloroformate, NEt_3, room temperature, 3 h; d) DMAP (30 mol%), toluene, 70 °C, 3 h; e) NaH, THF/DMF, 80 °C, 18 h, allyl bromide; f) LHMDS, THF, −78 °C, 7 h, BnBr. Bn = benzyl, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazide, LDA = lithium diisopropylamide.



Scheme 3. Manipulation of fluorous-tagged heterocycles—Pd-catalyzed modifications ($\mathbf{R^F} = C_8F_{17}CH_2CH_2$). Reagents and conditions: a) *m*CPBA, CH_2Cl_2, room temperature, 2 h; b) K_2CO_3, MeI, DMF, 40 °C, 2 h; c) $[Pd(PPh_3)_4]$, NEt_3, 80 °C, 18 h, propargyl alcohol or trimethylsilylacetylene and CuI (20 mol%); d) $[Pd(PPh_3)_3]$, Na_2CO_3, H_2O, dioxane, 80 °C, 3.5 h, $ArB(OH)_2$. *m*CPBA = *m*-chloroperbenzoic acid, TMS = trimethylsilyl.

purification, the desired product now eluting in the non-fluorous fraction. For the cleavage of fluorous sulfones, the fluorous component is lost to the aqueous layer during work up, and no purification is required (Scheme 4).

In conclusion, we have developed a new strategy for the high-throughput, fluorous-phase synthesis of N-heterocycle libraries. The sequence involves several key features: a fluorous-phase Pummerer cyclative-capture strategy for rapid access to tagged, heterocyclic frameworks; modification of the fluorous heterocyclic scaffolds by a variety of approaches, including Pd-catalyzed cross-coupling reactions; traceless, reductive removal of the fluorous phase tag. Studies on the application of this



Scheme 4. Products of reductive, traceless cleavage of the fluorous phase tag. (Compound **20** was obtained as a 1:1 mixture of tautomers according to NMR spectroscopic analysis).

strategy in solution-phase parallel and combinatorial library synthesis are currently underway.

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