Clean synthesis of α-bromo ketones and their utilisation in the synthesis of 2-alkoxy-2,3-dihydro-2-aryl-1,4-benzodioxanes, 2-amino-4-aryl-1,3-thiazoles and piperidino-2-amino-1,3-thiazoles using polymer-supported reagents

COMMUNICATION

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An array of 2-alkoxy-2,3-dihydro-2-aryl-1,4-benzodioxane derivatives and 2-amino-1,3-thiazoles were prepared in high yield using a straightforward three-step and two- step sequence of polymer-supported reagents, respectively and other polymer-supported sequestering reagents without any chromatographic purification step. A key step involves clean and efficient bromination of acetophenones using polymer-supported pyridinium bromide perbromide (PSPBP) and subsequent cyclisation reaction.

Due to the recent advances in the technologies surrounding high throughput screening, there is a pressing need for the generation of a large amount of diverse compounds. The demands are now focused on the development of clean and efficient methods for preparing compound libraries, rather than spending time on the purification of large libraries. Current methods involving the generation of chemical libraries using solid phase organic synthesis (SPOS) have struggled to meet these requirements alone and, to complement this strategy we have focused our efforts on the development of *orchestrated multi-step syntheses*, in the solution phase, using polymer-supported reagents. This approach combines the well-documented advantages of polymer-supported reactions as well as allowing the progressing reactions to be monitored by HPLC or TLC methods. The comprehensive use of polymer-supported reagents assisted by polymer-supported sequestering reagents, in the preparation of a wide variety of chemical entities, which involve no chromatographic purification step, have been reported from our laboratory.[1] Consequently, the development of our multi-step methods was recently exemplified in the six-step and ten-step linear syntheses of the natural products (±)-epimaritidine[2] and (±)-epibatidine,[3] respectively, using solely polymer-supported reagents to effect the individual steps and facilitate reaction clean-up. In this communication we wish to report further examples of the use of the polymer-supported reagents for the efficient construction of heterocyclic derivatives.

The wide variety of pharmaceutical properties associated with 1,4-benzodioxane derivatives includes seratonergic,[4] α_2-adrenoceptor,[5] antidepressant,[6] β-blocking[7] and antihypertensive[8] activity and hence makes these attractive molecules for synthesis programmes. Additionally, the 2-hydroxy-2-aryl-1,4-benzodioxanes have biological importance as potential fungicides[9] as well as exhibiting significant α_2-adrenoceptor antagonist[10] activity. Literature routes to 2-hydroxy-2-aryl-1,4-benzodioxanes are scarce and low yielding.[11] We envisaged a facile synthesis of an array of 1,4-benzodioxane derivatives could be achieved *via* the condensation of appropriately substituted 2-bromo-1-acetophenone derivatives with catechol using a polymer-supported base, such as polymer-supported carbonate.

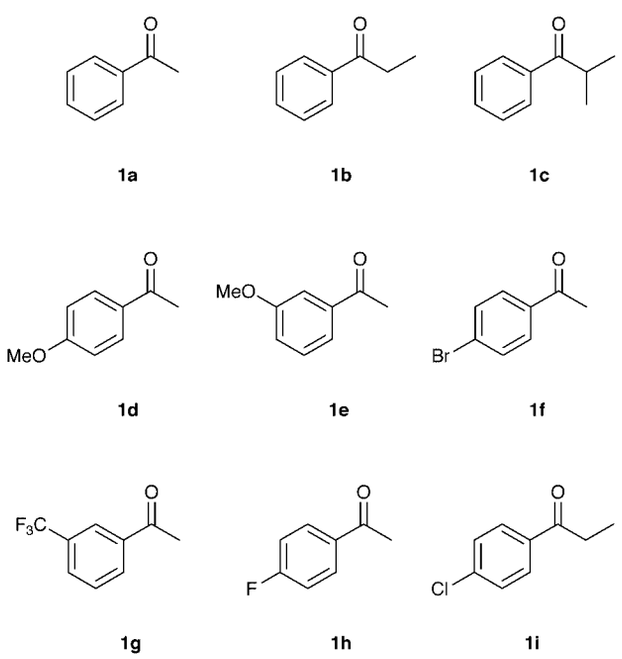
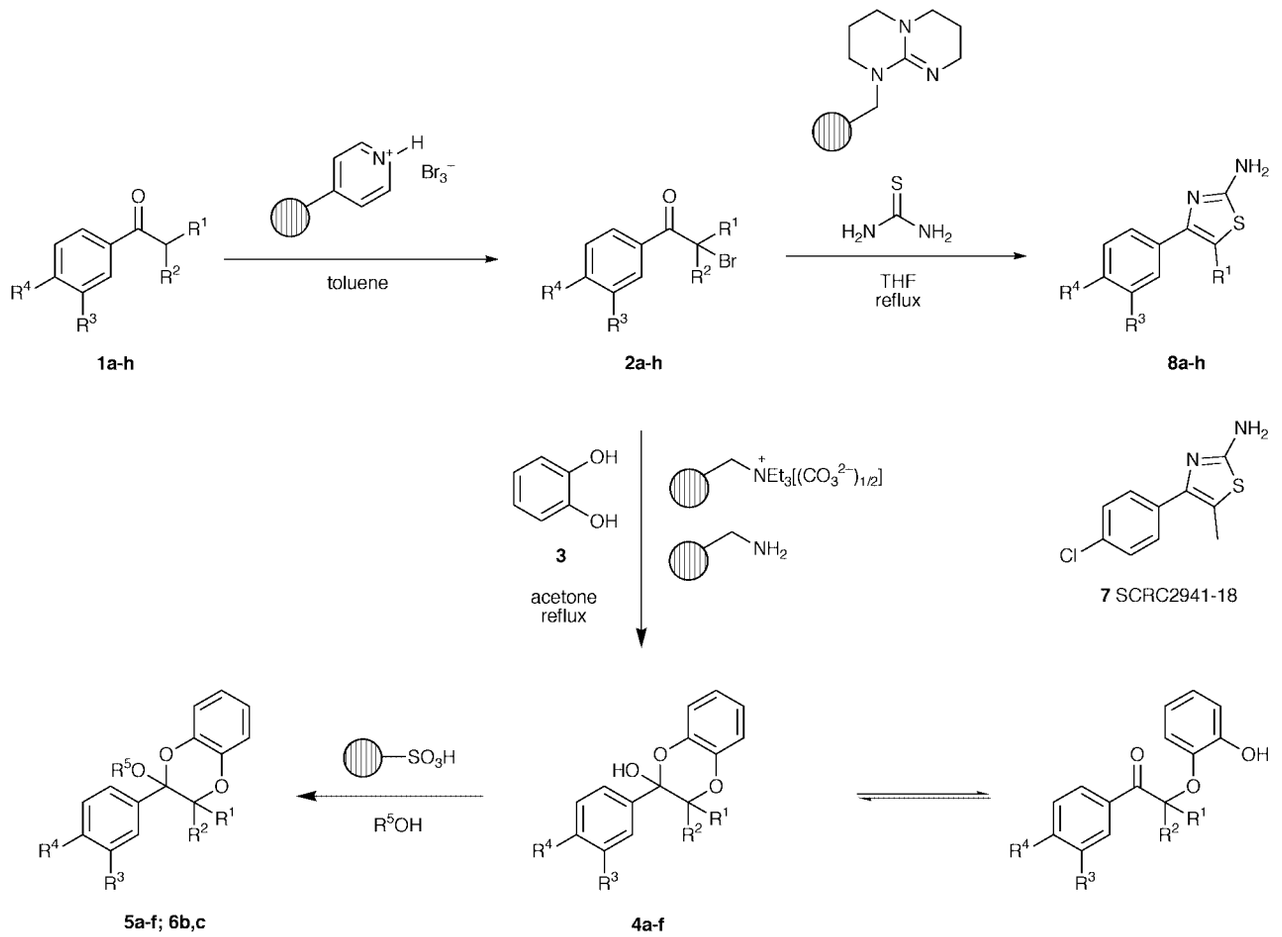


Fig. 1 Acetophenones brominated using PSPBP.

Our route to 1,4-benzodioxanes begins from the appropriate commercially available acetophenones **1a**–**h** (Fig. 1) which were initially brominated α to the keto-function using polymer-supported pyridinium bromide perbromide (PSPBP) in toluene at 10 °C (Scheme 1).[1e,12] The α-bromo ketones **2a**–**h** were obtained in pure form simply by filtration of the mixture to remove the spent polymer-supported reagent followed by evaporation of the solution. α-Bromo ketones are versatile intermediates and we have recently reported their use in the convergent synthesis of an array of substituted benzofurans,[12] and piperidino-thiomorpholines[1e] in other synthesis programmes. Next, the α-bromo ketones **2a**–**f** were treated with an equimolar quantity of catechol **3** in dry acetone followed by the addition of two equivalents of polymer-supported carbonate[13] to afford the 2-hydroxy-2-aryl-1,4-benzodioxanes **4a**–**f** in quantitative yield as a mixture of the open chain and ring closed tautomer.[9b–e,14] Best results were obtained by heating the mixtures under reflux in anhydrous acetone for 12 h along with vacuum dried carbonate resin, although shorter reaction times (1 h) with greater relative amounts of polymer-supported carbonate (five equivalents) did allow near complete conversion to the desired products. In all cases, work-up involved addition of aminomethyl polystyrene (one equivalent) which acted as a



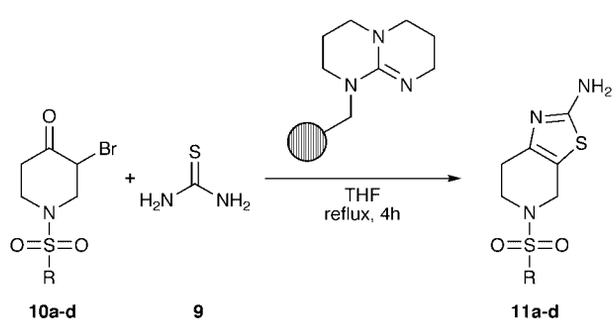
Scheme 1

dual polymer-supported sequestration reagent to remove any unreacted acidic catechol **3** and also any trace of remaining α-bromo ketone **2a**–**f**. Further elaboration of this array of compounds **4a**–**f**, included a trans-acetalisation reaction effected by treatment with the acidic resin DOWEX 50 (H^+ form) by refluxing the mixture in either methanol or ethanol (R^5OH in Scheme 1) for 12 h. The product 2-alkoxy-2,3-dihydro-2-aryl-1,4-benzodioxanes **5a**–**f** (R^5 = Me) and **6b**,**c** (R^5 = Et) were obtained in pure form as determined by LC-MS, ^1H and ^{13}C NMR spectroscopic analysis.

The 1,3-thiazole functionality appears in a diverse range of natural products and is present in a vast number of molecules which have potent biological activity.[15] Recently, 2-amino-4-phenyl-1,3-thiazole derivatives were found to inhibit the Interleukin-6 (IL-6) induction stimulated by parathyroid hormone (PTH) in osteoblastic MC3T3-E1 cells, with SCRC2941-18 **7** (IC_{50} = 1.0 μg cm^{-3}) found to be the most potent inhibitor.[16] In addition 4-phenyl-1,3-thiazole derivatives are expected to become important targets in medicine as potential treatments for multiple myeloma, chronic autoimmune disease as well as AIDS.[16]

Therefore, we have implemented an efficient and simple route to 2-amino-4-aryl-1,3-thiazoles **7**, **8a**,**d**,**g**,**h** (Scheme 1). Direct treatment of α-bromo acetophenones **2a**,**d**,**g**,**h**,**i** with thiourea **9** in the presence of polymer-supported 1,5,7-triazabicyclo[4.4.0]-dec-5-ene (TBD-P)[17] as base, in refluxing THF for 30 minutes, effected cyclodehydration to the desired products.[18] It was found that the aryl substituent had a significant effect on the yield of the reaction with electron-withdrawing groups giving higher yields although the purities of the products were not compromised.

To show the capability of our split-and-divert concept, we obtained α-bromo ketone intermediates by intercepting another reaction stream.[1e] From our synthesis of piperidino-thiomorpholines we took four sulfonamidated α-bromo piperidones **10a**–**d** which were treated over 4 hours with thiourea **9** in the presence of TBD-P in refluxing THF (Scheme 2). The corresponding 2-amino-1,3-thiazoles **11a**–**d** were obtained in high yields and high purities.



R: **a** = 4-tolyl, **b** = 3-(trifluoromethyl)phenyl, **c** = 4-fluorophenyl, **d** = 2-thiophenyl

Scheme 2

In conclusion we have developed a clean three-step preparation of 2-alkoxy-2,3-dihydro-2-aryl-1,4-benzodioxanes **5** without any chromatographic purification step to demonstrate the versatility of the orchestrated application of polymer-supported reagents and sequestration agents in synthetic sequences. Each step produced essentially clean products and the intermediate α-bromo ketones **2a**–**h** could be used in other synthesis programmes, such as the preparation of the 2-amino-4-aryl-1,3-thiazoles **7**, **8a**,**d**,**g**,**h** upon treatment with thiourea and TBD-P. Intermediates from other synthesis programmes could be introduced successfully into this synthesis programme to give the piperidino-2-amino-1,3-thiazoles **11a**–**d**. Yields and purities of all compounds prepared are presented in Table 1.

Table 1 Summary of polymer-supported reactions

	Yield (%)	Purity (%)	M^+ (ES-MS)		Yield (%)	Purity (%)	(ES-MS)
2a	90	>95	201.10 (+)	**5b**	98	>95	[a]
2b	70	>95	215.10	**5c**	90	95	[a]
2c	75	>95	[a]	**5d**	94	>95	[a]
2d	89	93	231.00	**5e**	96	>95	[a]
2e	92	92	231.00	**5f**	>95	>95	291.00
2f	95	>95	[a]	**6b**	95	94	211.21
2g	92	93	266.91	**6c**	95	>95	284.92
2h	80	>95	218.00	**8a**	81	>95	177.10
2i	68	>95	[a]	**7**	94	>95	226.2
4a	95	95	211.17	**8d**	47	95	207.21
4b	95	>95	226.90	**8g**	>95	95	245.18
4c	90	95	239.26	**8h**	80	>95	195.16
4d	90	93	257.11	**11a**	95	>90	310.09
4e	95	95	257.04	**11b**	73	>85	364.19
4f	98	>95	307.00	**11c**	>95	>95	314.17
5a	>95	>95	211.20	**11d**	>95	>90	302.06

[a] No mass ion could be observed under ES-MS conditions.

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14 By treating a mixture of the open- and closed-chain tautomers (0.5 mmol) in refluxing anhydrous THF (5. 0 cm^3) with DOWEX 50 (H^+ form, 1.0 g) for 6 h, the closed-chain 2-hydroxy-2-aryl-1,4-benzodioxanes **4a**–**f** were the only products obtained. In some cases the pharmacologically active form was found to be the open-chain tautomer, *e.g.* the phytotoxic form as fungicides [ref. 9(*a*)]; or the closed-chain tautomer, *e.g.* the blood-pressure lowering benzodioxane derivatives (ref. 8). Systematic surveys of the electronic effects of substitents on the 2-aryl ring on the ring-chain tautomerism have been reported [ref. 9(*b*)–(*e*)].

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18 The cycloaddition of **2b**,**c**,**i** with thiourea **9** required heating in refluxing THF for 24 h. The formation of aminothiazoles **8e**,**f** could also be effected by stirring at room temperature for 15 minutes in acetonitrile.

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