PERKIN 1 COMMUNICATION

Clean five-step synthesis of an array of 1,2,3,4-tetra-substituted pyrroles using polymer-supported reagents

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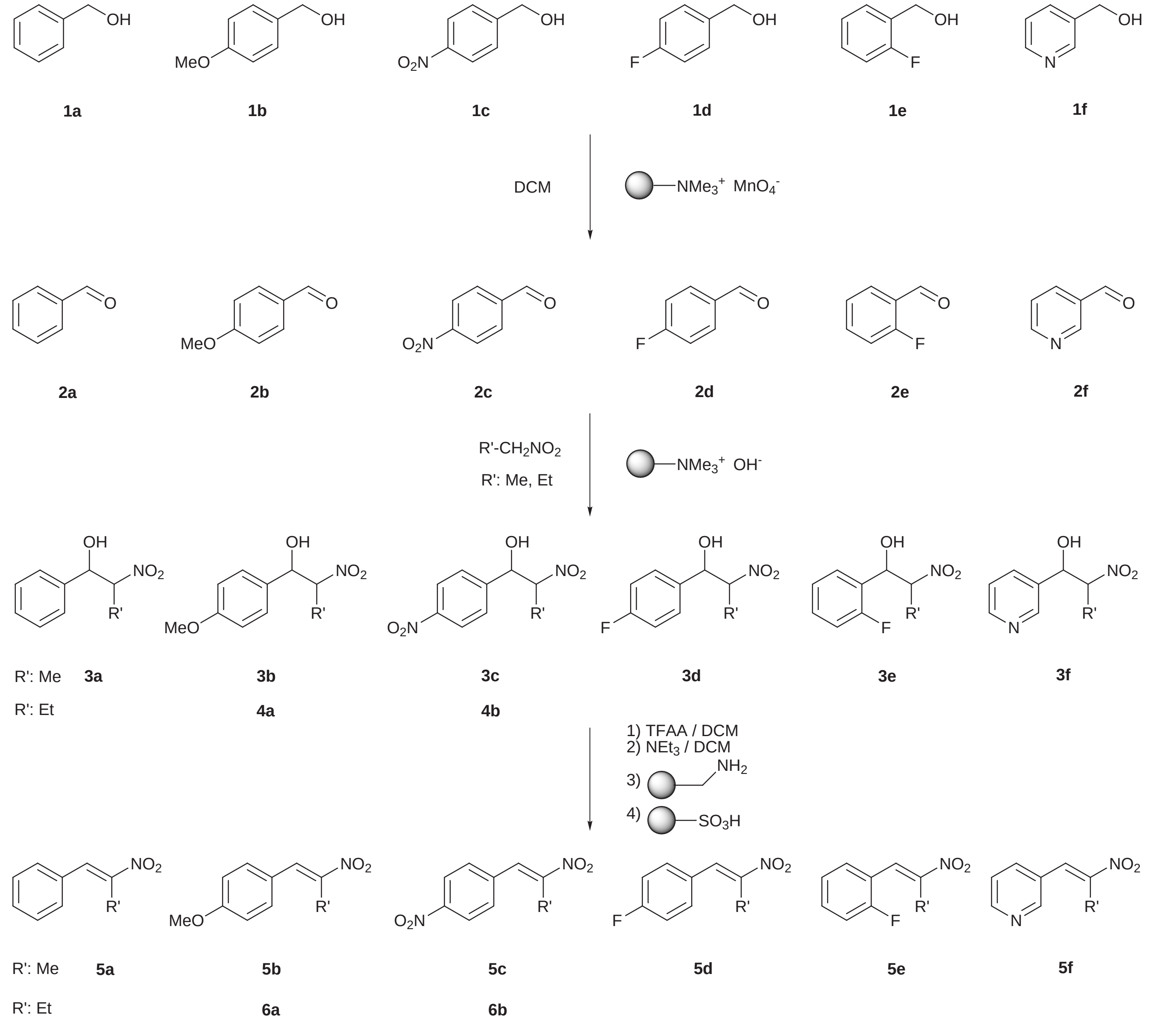
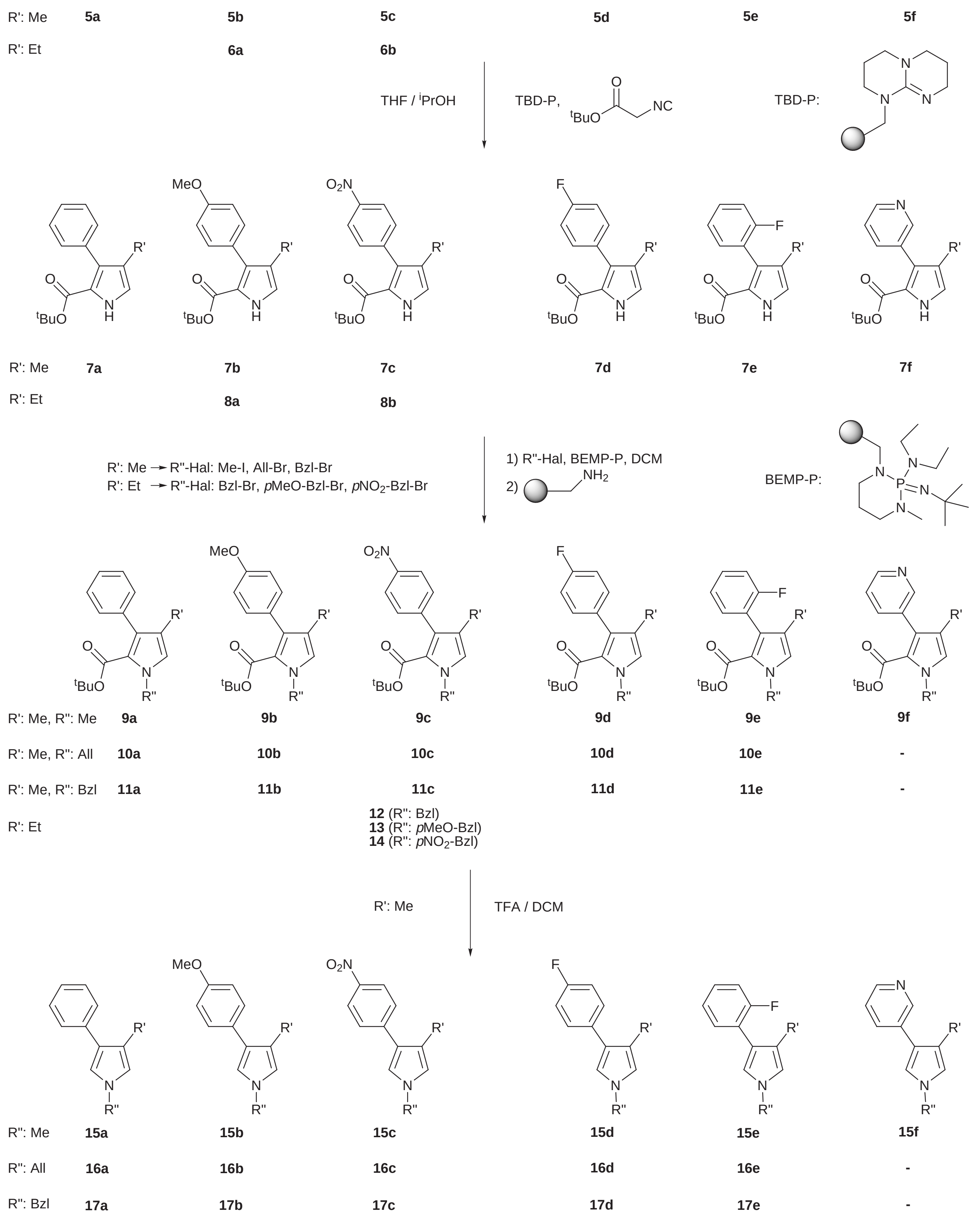
Polymer-supported reagents and other solid sequestering agents may be used to generate an array of 1,2,3,4-tetra-substituted pyrrole derivatives without any chromatographic purification step.

The capability of high throughput screening of potential drug substances is placing ever increasing demands on the methods for the fast and efficient generation of new chemical entities. In general, chemical libraries or arrays, containing large numbers of compounds, may be prepared either on polymer supports or in solution.[1a] The advantages of polymer-supported reactions (*e.g.* allowing the application of a large excess of the reagent without the need for additional purification steps) and the benefits of solution phase chemistry (*e.g.* the ease of monitoring the progress of the reactions by applying LC-MS, TLC or NMR techniques) can be combined by using polymer supported reagents. While solid-supported reagents have been described over many years,[1a–d] only a few of these have been used in combinatorial chemistry.[2a–e] Furthermore, *multi-step reaction* sequences using polymer-supported reagents are rare,[3] although there is a growing interest in the use of sequestering agents on solid supports.[2e,4] Recent work in our group has



Scheme 1



Scheme 2

focussed on the development of orchestrated multi-step methods using polymer-supported reagents for the preparation of chemical compound libraries.[5] In this communication we wish to report a further example using various supported reagents for the efficient construction of heterocyclic derivatives.

Pyrrole derivatives have found applications in medicine and agriculture.[6] Therefore, the development of a fast and flexible method to generate libraries of such compounds was desirable. We have designed a route to 1,2,3,4-tetra-substituted pyrroles as potentially interesting chemical scaffolds using a series of polymer-supported reagents.

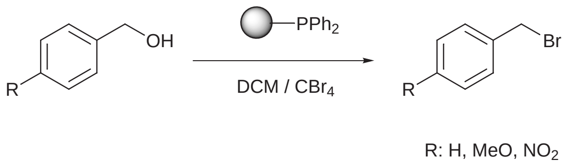
Starting from a range of commercially available benzylic alcohols **1a**–**f** an oxidation reaction was carried out using polymer supported permanganate (PSM) in dichloromethane (Scheme 1) to furnish the benzaldehydes **2a**–**f**.[7] Alternatively, this reaction can be carried out using polymer supported perruthenate (PSP).[5a] The next step of the process employs Amberlite IRA-420 (OH) as a strong polymer-supported base to effect the Henry reaction with nitroalkenes.[8] This reaction must

Table 1 Summary of polymer-supported reactions

	Yield (%)[a]	LC-Purity (%)	ES-MS[b]		Yield (%)[a]	LC-Purity (%)	ES-MS[b]
2a	95	>95	—	**10b**	70	>98	272.07 (+)
2b	95	>95	—	**10c**	60	>95	286.99 (+)
2c	95	>95	—	**10d**	Quant.	>98	260.07 (+)
2d	95	>95	—	**10e**	Quant.	>98	260.07 (+)
2e	95	>95	—	**11a**	Quant.	>92	292.22 (+)
2f	95	>95	—	**11b**	77	>98	322.28 (+)
5a	27	>95	—	**11c**	89	>95	337.19 (+)
5b	23	>95	—	**11d**	Quant.	85	310.22 (+)
5c	45	>98	—	**11e**	Quant.	>98	310.05 (+)
5d	60	>98	—	**12**	Quant.	>95	351.20 (+)
5e	65	>95	—	**13**	Quant.	>95	437.17 (+)
5f	40	>98	—	**14**	Quant.	>95	450.13 (−)
6a	25	90	—	**15a**	Quant.	>98	169.86 (+)
6b	77	92	—	**15b**	Quant.	>95	187.08 (+)
7a	Quant.	>95	203.07 (+)	**15c**	Quant.	>98	200.07 (+)
7b	Quant.	>98	233.20 (+)	**15d**	Quant.	>98	175.46 (+)
7c	Quant.	>98	301.19 (−)	**15e**	Quant.	>98	174.98 (+)
7d	Quant.	>98	202.05 (+)	**15f**	Quant.	90	173.11 (+)
7e	96	>98	201.99 (+)	**16a**	Quant.	>98	240.94 (−)
7f	97	>98	259.29 (+)	**16b**	Quant.	>95	198.11 (+)
8a	83	>95	247.20 (+)	**16c**	Quant.	>95	228.20 (+)
8b	Quant.	>98	261.10 (+)	**16d**	Quant.	>98	216.14 (+)
9a	Quant.	>98	198.10 (+)	**16e**	Quant.	>95	216.15 (+)
9b	Quant.	>95	246.11 (+)	**17a**	Quant.	>95	247.95 (+)
9c	Quant.	>98	261.08 (+)	**17b**	Quant.	>95	278.12 (+)
9d	76	>98	233.90 (+)	**17c**	Quant.	>95	293.16 (+)
9e	Quant.	>98	234.09 (+)	**17d**	Quant.	>98	266.09 (+)
9f	82	92	217.09 (+)	**17e**	Quant.	>98	266.19 (+)
10a	75	>98	242.09 (+)				

[a] Yields for reaction from precursor compound. [b] Masses given are obtained in the mode denoted in brackets. Mass ions are generally M + H, M − H or in some cases M + H − Butyl. For some of the products, no mass ion could be observed under ES-MS conditions. For those compounds, characterisation by ^{1}H NMR was regarded as sufficient.

be performed using a large excess of the nitro compound (normally used neat),[9] in order to give the nitroaldol condensation products **3a**–**f** and **4a**,**b** in a very clean fashion. To facilitate the elimination of these 1-hydroxy-2-nitro compounds they were treated with 50% trifluoroacetic acid anhydride in dichloromethane resulting in the formation of the corresponding trifluoroacetates, which were subsequently reacted with triethylamine and gave the nitrostyrene derivatives **5a**–**f** and **6a**,**b**. The work-up of this reaction involved treatment with aminomethyl polystyrene and acidic Amberlyst A-15. The heterocyclic pyrrole ring system was then constructed by a clean 1,3-dipolar cycloaddition of *tert*-butyl isocyanoacetate and the nitrostyrenes (**5a**–**f**, **6a**,**b**) in the presence of the polymer supported guanidine base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in a 1:1 mixture of tetrahydrofuran and propan-2-ol to yield the compounds **7a**–**f** and **8a**–**b** (Scheme 2).[10,11] Further substitution at the hetero atom in these compounds could be achieved by reacting the pyrroles with an excess of an alkyl halide in the presence of a polymer-supported phosphazene base to yield the derivatives **9a**–**f**, **10a**–**e** and **11a**–**e**.[12,13] After completion of the reaction, the excess of the halide was sequestered with aminomethyl polystyrene in the normal way. A set of alkyl bromides used in the work could be prepared easily by reacting alcohols and carbon tetrabromide with polymer-bound triphenylphosphine[14] (Scheme 3) and is illustrated for the preparation of benzyl bromide, *p*-methoxybenzyl bromide and *p*-nitrobenzyl bromide, which were then applied in the synthesis of the pyrrole derivatives **12**, **13** and **14**. For further elaboration of this array of compounds, the *tert*-butyl ester could be cleaved by treatment with trifluoroacetic acid, upon which instantaneous decarboxylation afforded the pyrroles **15a**–**f**, **16a**–**e** and **17a**–**e**.



Scheme 3

In conclusion we have generated an array of 19 1,2,3,4-tetrasubstituted (**9a**–**f**, **10a**–**e**, **11a**–**e**, **12**, **13**, **14**) and 16 1,3,4-trisubstituted (**15a**–**f**, **16a**–**e**, **17a**–**e**) pyrrole derivatives without any chromatographic purification step to demonstrate the versatility of the orchestrated application of polymer-supported reagents and sequestering agents in synthetic sequences. Many further analogues could, in principle, be generated by this route. All reactions produced essentially clean products, as was shown by LC-MS and NMR-spectroscopy. All intermediates could also be isolated by intercepting part of the reaction streams and used in other synthesis programmes. Yields and purities of the various compounds are given in Table 1.

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7 Prepared by filtering an aqueous solution of potassium permanganate through Amberlyst A-27, subsequent washing of the obtained brick-red material with water and acetone and drying of the beads *in vacuo.*

8 The utilisation of Amberlyst A-21 for a similar reaction has been described (G. Rosini, R. Ballini and M. Petrini, *Synthesis*, 1986, 46), but this ion exchange resin proved to be not very efficient in our hands. Instead of Amberlite IRA-420 (OH-form), DOWEX-1 (OH-form) can be used.

9 Without an excess or in absence of the nitromethylene compound Amberlite IRA-420 (OH-form) can effect a Cannizzaro reaction of electron-poor benzaldehydes. In combination with a solid supported oxidant to reoxidise the benzylic alcohols to the aldehydes, this reaction can be used to generate benzoic acids.

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11 TBD on polystyrene was 2.2 mmol g^{-1} and purchased from Fluka. In the reaction 1.1 equiv. of the isocyanide and 2 equiv. of the base were used.

12 BEMP on polystyrene was 2.3 mmol g^{-1} and purchased from Fluka. In the reaction 5 equiv. of the alkyl halide and 20 equiv. of the base were used.

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