COMMUNICATION

Clean three-step synthesis of 4,5-dihydro-1*H*-pyrazoles starting from alcohols using polymer supported reagents

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Nafion-TMS mediated Mukaiyama aldol reaction of silyl enol ethers with aldehydes, obtained from mild oxidation of alcohols with polymer supported perruthenate (PSP), yielded α,β-unsaturated ketones, which upon treatment with hydrazines allowed the clean synthesis of 4,5-dihydro-1*H*-pyrazoles.

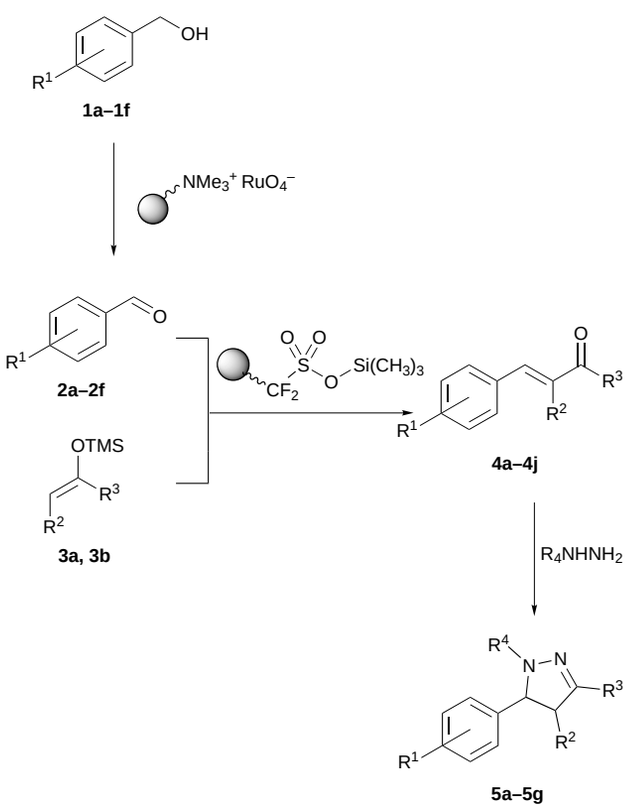
The growing need for compound libraries, especially for biological evaluation, has led to an increasing demand for clean and efficient syntheses of complex organic molecules. In general, such libraries are prepared either on a solid support or in solution. The use of solid supported reagents however combines the advantages of allowing the use of an excess of the reagent without the need for an additional purification step, and also permits simple analysis of the progressing reactions. Despite the many reagents that have been developed on solid supports,[1] their application in *multi-step* syntheses of chemical libraries has received only little attention so far.[2] In this communication we wish to report our first example of such an orchestrated *multi-step* synthesis of a chemical library using polymer supported reagents.

1*H*-Pyrazoles and 4,5-dihydro-1*H*-pyrazoles have found diverse applications in medicine and agriculture. In particular, they are known as potent antibiotic and antioxidant agents.[3] Hence, methods capable of generating libraries of heterocycles of this type are very attractive. We therefore devised a synthesis of 4,5-dihydro-1*H*-pyrazoles using polymer supported reagents.

4,5-Dihydro-1*H*-pyrazoles are often synthesized by treating α,β-unsaturated ketones with hydrazines.[4] The reaction of choice for the preparation of unsaturated ketones is the Mukaiyama aldol condensation using various Lewis acid catalysts.[5] However, in solution these condensation procedures often involve strongly acidic and thermal conditions which are not always compatible with sensitive functional groups in the target molecule, and more importantly, are not suitable for automation. A polymer supported version of the Mukaiyama aldol addition using lanthanide-resins as catalysts has been reported recently,[6] nevertheless a protocol leading *directly* to the elimination product was still missing.

Also in evaluating any starting material for combinatorial chemistry, special attention must be directed to the ready availability of a broad variety of appropriate monomer sets of building blocks. While a large number of alcohols are commercially available the same is not true for aldehydes even though these are attractive starting materials for a large range of chemical transformations.

Our route to 4,5-dihydro-1*H*-pyrazoles therefore starts with alcohols which are firstly oxidised to the corresponding aldehydes *in situ* using polymer supported perruthenate (PSP).[7] Next a polymer supported Mukaiyama aldol condensation is envisaged using silyl enol ethers which are coupled with the synthesised aldehydes to generate α,β-unsaturated ketones that on subsequent treatment with hydrazines should lead to the desired 4,5-dihydro-1*H*-pyrazole scaffold (Scheme 1).

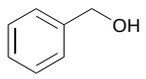
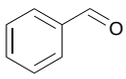
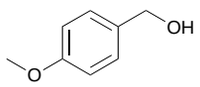
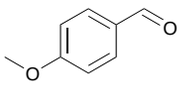
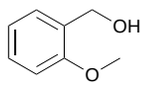
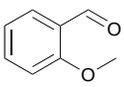
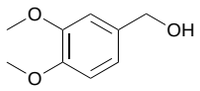
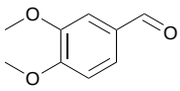
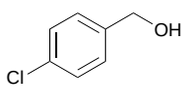
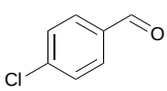
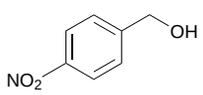
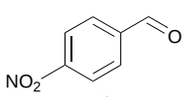


Scheme 1

Recently we have shown the use of this polymer supported perruthenate (PSP) as a mild oxidant for the clean conversion of primary alcohols to the corresponding carbonyl compounds under catalytic oxidation conditions with air[8] and in the oxidation of hydroxylamines to nitrones.[9] Table 1 summarises an extension of these previous studies yielding those aldehydes needed for this study. In a typical experiment, the alcohol (0.2 mmol) was added to a mixture of PSP (0.6 mmol) in 2.5 ml dichloromethane at room temperature. Work-up consisted of filtration followed by evaporation *in vacuo* without any further chromatographic purification. In general, the alcohols were converted quantitatively into their corresponding aldehydes within 16 hours. These aldehydes were then used directly in the next Nafion-TMS mediated Mukaiyama aldol reactions with silyl enol ethers to yield the corresponding unsaturated carbonyl compounds.

Naifon-TMS shows remarkable abilities not only as a powerful silylating agent[10] but also as a Lewis acid in aldol couplings. In our hands, this reagent allowed the clean coupling of silyl

Table 1 Oxidations of alcohols **1a**–**1f** to aldehydes **2a**–**2f** using PSP[a]

Alcohol	Aldehyde	Reaction time/h	GLC yield[b] (%)
 **1a**	 **2a**	5	>95
 **1b**	 **2b**	5	>95
 **1c**	 **2c**	48[c]	>95
 **1d**	 **2d**	16	>95
 **1e**	 **2e**	16	>95
 **1f**	 **2f**	5	>95

[a] Reaction conditions: 3 equiv. PSP, CH_2Cl_2, rt. [b] As judged by NMR analysis of the crude product the purity in all entries was >95%. [c] After 24 h two more equivalents of PSP were added.

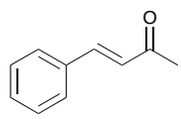
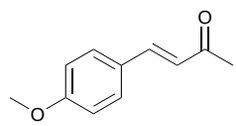
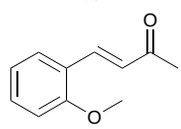
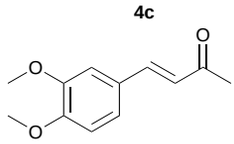
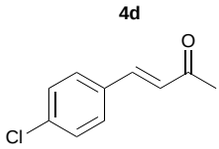
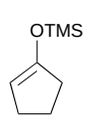
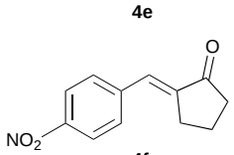
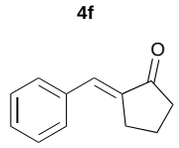
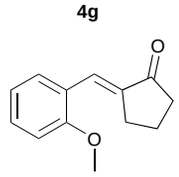
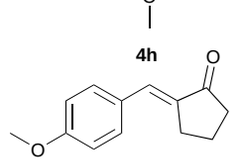
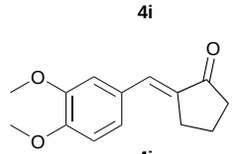
enol ethers to aldehydes to yield aldol products which reacted further to lead directly to α,β-unsaturated ketones.

Thus the aldehyde (0.2 mmol) was added to a mixture of Nafion-TMS (0.6 mmol) and 4 Å molecular sieves as dehydrating agent, in dichloromethane (3 ml) at −78 °C followed by addition of the trimethylsilyl enol ether (0.2 mmol) which was then allowed to slowly warm to room temperature. The work-up consisted only of filtration followed by evaporation *in vacuo*. No further purification was needed. The results of a number of these reactions are summarised in Table 2. Using 2-(trimethylsilyloxy)propene **3a** the aromatic aldehydes were cleanly transformed into the corresponding enones overnight. No other product could be detected by GLC analysis. In general, the coupling with 1-(trimethylsilyloxy)cyclopentene **3b** proceeded slightly less efficiently and some cyclopentanone was observed as decomposition product. While the yield for the aldol condensation was generally around 95% in many cases, aldehydes bearing electron withdrawing groups coupled slowly. No attempt was made to optimise these reactions.

Lastly, the above α,β-unsaturated ketones were treated with hydrazine[11] or methylhydrazine to give the final products. The crude enone (0.2 mmol) was dissolved in absolute ethanol (2 ml) and 1.0 equivalent of hydrazine or methylhydrazine was added. Upon consumption of the starting material, as indicated by GLC, the solvent was removed by evaporation *in vacuo* and the products were analysed by NMR spectroscopy. All 4,5-dihydro-1*H*-pyrazoles synthesised were obtained in good yields and high purities (Table 3).

Due to the high yielding nature of both the solid supported

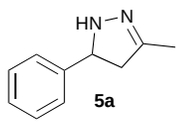
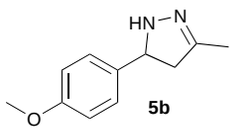
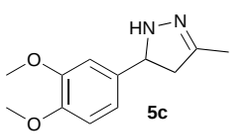
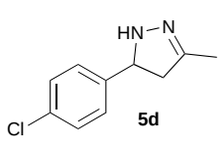
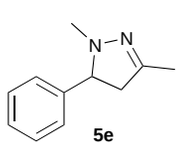
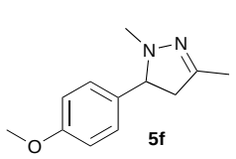
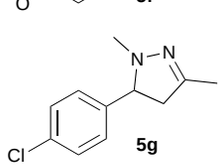
Table 2 Nafion-TMS mediated Mukaiyama aldol reactions of aldehydes **2a**–**2f** and silyl enol ethers **3a** and **3b** yielding enones **4a**–**4j**[a]

Enol ether	Aldehyde	Enone[b]	Reaction time/h	GLC yield (%)
3a	**2a**	 **4a**	18	>95[c]
"	**2b**	 **4b**	20	>95[c]
"	**2c**	 **4c**	20	>95[c]
"	**2d**	 **4d**	24	95[c]
"	**2e**	 **4e**	36	>95[c]
 **3b**	**2f**	 **4f**	20	8
"	**2a**	 **4g**	20	15
"	**2c**	 **4h**	40	48
"	**2b**	 **4i**	40	54
"	**2d**	 **4j**	40	95[c]

[a] Reaction conditions: 3 equiv. Nafion-TMS, CH_2Cl_2, −78 °C to rt. [b] Enones were satisfactorily identified by their ^1H and ^{13}C NMR spectra and where possible by comparison with authentic samples. [c] As judged by NMR analysis of the crude product the purity was >85%.

processes (oxidation and aldol coupling) as well as the condensation with hydrazine reagents in the final step, the synthesis sequence proceeds without any intermediate tedious work-up procedures. Between the individual steps throughout the whole process, the only purification step needed to afford pure

Table 3 Synthesis of 4,5-dihydro-1*H*-pyrazoles **5a**–**5g** starting from enones **4a**–**4e**[a]

Enone	Hydrazine	4,5-Dihydropyrazole[b]	Reaction time/h	GLC yield[c] (%)
4a	$NH_2NH_2{\cdot}H_2O$	 **5a**	3	>95
4b	$NH_2NH_2{\cdot}H_2O$	 **5b**	3	92
4d	$NH_2NH_2{\cdot}H_2O$	 **5c**	3	92
4e	$NH_2NH_2{\cdot}H_2O$	 **5d**	3	94
4a	CH_3NHNH_2	 **5e**	3	>95
4b	CH_3NHNH_2	 **5f**	3	94
4e	CH_3NHNH_2	 **5g**	3	92

[a] Reaction conditions: 1 equiv. hydrazine in abs. ethanol, rt. [b] 4,5-Dihydropyrazoles were satisfactorily identified by their ^1H and ^{13}C NMR spectra and where possible by comparison with authentic samples. [c] As judged by NMR analysis the purity in all entries was >85%.

products consists of a mere filtration of the reaction mixture in order to remove the functionalised polymers.

In conclusion we have developed a new clean *multi-step* preparation of 4,5-dihydro-1*H*-pyrazoles starting from alcohols which we believe to be suitable for robotic synthesis procedures. The route clearly demonstrates the considerable potential the orchestrated combination of several polymer supported reagents has for the preparation of chemical libraries. When these reagent based methods are combined with the recent polymer supported sequestration[12] and capture[13] techniques even greater opportunities present themselves.

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