Pergamon

Tetrahedron Letters 39 (1998) 4125–4128

TETRAHEDRON
LETTERS

Supported phenolates as efficient catalysts of the Michael reaction.

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Received 18 February 1998; accepted 27 March 1998

Abstract: Simple, heterogeneous base catalysts based on supported phenolates can be easily prepared and are very active and selective in the Michael reaction.

Keywords: Michael reaction, Catalysis, Supported Reagents/reactions

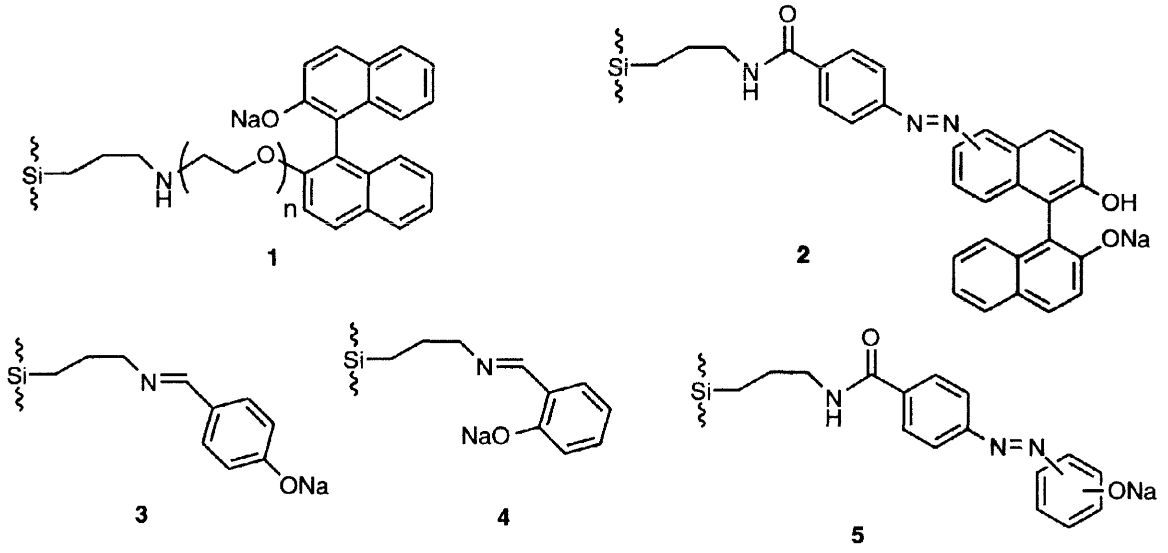
Introduction

The search for novel heterogeneous catalysts is one of the major themes of Waste Minimisation. Much progress has been made in the fields of oxidation and acid catalysis recently, but the development of mild, efficient solid bases, has been less intensively studied. As part of a research programme centred on chemically modified surfaces as novel heterogeneous catalysts[1], we have recently demonstrated that aminopropyl functionalised silica (AMPS)[2] and MCM-type materials (AMP-HMS)[3] are efficient catalysts for the Knoevenagel reaction. These materials are, however, less well suited to the Michael addition. KF-alumina, which has been reported as being an excellent Michael catalyst, suffers from lack of reproducibility[4]. We have recently reported supported racemic BINOLate catalysts which are active in the Michael reaction[5]. We would now like to present our results relating to simple phenolates immobilised on silica as efficient base catalysts for the Michael reaction.

While the BINOLate species **1** and **2** show high conversions and good reusability in the addition of β-ketoesters to enones[5], their cost is too high for non-enantioselective applications. In addition, reaction times are relatively long. We have therefore prepared a series of catalysts, based on simpler phenolates, with a view to finding more active catalysts. We have used a variety of coupling procedures to attach the phenolates to the surface. The simplest methodology involves the use of aminopropyl-substituted silicas (AMPS). Reaction of AMPS with aldehydes is known to result in supported imines in a very efficient, mild reaction.[6,7] Reaction of *o*- and *p*-hydroxybenzaldehydes with AMPS in ethanol resulted in the formation of supported phenolates **3** and **4**. Following the disappearance of the phenol by UV-Vis spectroscopy of the supernatant liquid indicated that reaction was complete within approximately one minute at room temperature. No other absorbance was detected even after prolonged stirring, indicating that no imine was being leached from the catalyst.

PII: S0040-4039(98)00672-8

A second type of supported phenolate **5** was accessed via diazonium chemistry[8]. These catalysts were screened, along with the BINOLate catalysts described previously.



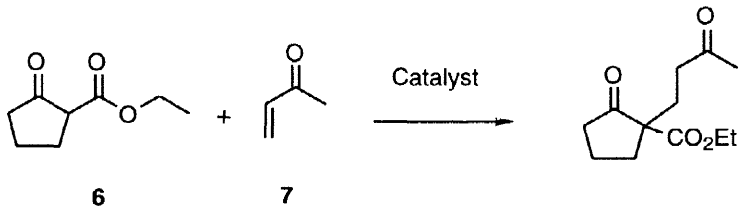
Scheme 1. Catalysts studied

Experimental

Preparation of **3**. AMPS[2] (5g) was stirred at 20°C with 4-hydroxybenzaldehyde (1.22g, 10mmol) in ethanol (50mL). After 1 minute, the reaction mixture was filtered and the solid washed with ethanol. The solid was stirred with 1.00g $NaHCO_3$ in 1:1 water /methanol for 1h and filtered, washed with water (3x50mL), methanol (2x50mL) and finally dried at 100°C.

Reaction of **6** with **7**. **6** (1.56g, 10mmol) and **7** (1.10g, 14mmol) were added to a suspension of **3** (0.025g, 0.25mol% phenolate) in ethanol (10mL). The mixture was stirred for 0.25h at 20°C. The reaction was worked up by filtration and removal of solvent to give the crude product, which was further purified by conventional means.

Results and Discussion



Catalyst	Time (h)	conversion(%)[a]
1	20	61
2	20	55
3	0.25	99
4	40	21
5	40	97

Table 1. Preliminary screening of supported phenolates.

(a): GC with internal standard (*n*-dodecane). Conversion based on ketoester, side products include dimers and oligomers of 3-butene-2-one. Initial ratio of **6** : **7** = 1 : 1.4

The initial screening was carried out using the reaction of ethyl 2-oxocyclopentane carboxylate (**6**) with 3-butene-2-one (**7**) in ethanol at room temperature. (Table 1)

Similar results were obtained with ethyl 2-oxocyclohexane carboxylate (**8**). From these initial results, it is clear that **3** is by far the most active catalyst out of the five studied. The loading of the catalyst is relatively high (0.9mmol g^{-1}) compared to the others (0.2-0.5mmol g^{-1}); however, the dramatically enhanced activity is likely to be mostly due to the ease of access to the phenolate centre in **3** compared to the other, more hindered species.

Having defined the optimum catalyst, other reactions were studied. These were chosen to include not only C-nucleophiles,(nitromethane, **9** and ethyl cyanoacetate, **10**) but also N-(piperidine, **11**) and S- based (thiophenol, **12**) systems. The range of acceptors was also extended to include cyclohexenone, **13**, methyl acrylate (**14**) and methyl methacrylate (**15**). The results are tabulated in Table 2.

Reactants		Solvent	Conditions, h(°C)	Conversion[a]
6	**7**	EtOH	0.25 (20)	99
8	**7**	EtOH	0.33 (20)	97
10	**7**	EtOH	3 (20)	76[b]
9	**7**	EtOH	1 (20)	88
12	**7**	EtOH	0.05(20)	93[c]
12	**13**	EtOH	0.033 (20)	99
9	**13**	$MeNO_2$	2 (100)	71
6	**13**	EtOH	4 (80)	0.5
10	**13**	EtOH	4 (80)	37[d]
10	**13**	EtOH	3 (80)	86[e]
12	**14**	EtOH	18(20)	96[f]
10	**14**	EtOH	18(80)	5
9	**14**	EtOH	18(80)	2.5
6	**14**	EtOH	18(80)	10[g]
12	**15**	EtOH	18(25)	42[h]
11	**15**	EtOH	4(80)	58
10	**15**	EtOH	18(80)	0
9	**15**	EtOH	18(82)	0.5
6	**15**	EtOH	18(80)	5

(a) GC yields with internal standard. Isolated yields are 5-10% lower, unless otherwise stated. All reactions (except those involving **7**) were run at a 1 : 1 ratio of reagents (but see footnote e). Those involving **7** were run with a 40% excess of **7**.

(b) Mono : di alkylation = 1 : 1.15

(c) Reaction in absence of catalyst gave 24% conversion after this time

(d) Mono : di = 2.2 : 1: diastereomeric ratio = 13 : 1. Products not isolated.

(e) ratio of **10** : **13** = 2 : 1; Mono : di = 3.4 : 1; diastereomeric ratio = 10.4 : 1. Isolated yield of mono-products = 56%

(f) Reaction in absence of catalyst gave 4% conversion after 18h. Disulphide present (2.5%)

(g) Remainder of methyl acrylate had polymerised

(h) disulphide present at 15% level

(i) No catalyst - 22% conversion under the same conditions

Table 2. Results from Michael reactions catalysed by **3**.

As can be seen, **3** catalyses the reaction of S-, N- and C- centred nucleophiles in a highly selective manner. Unless otherwise stated the uncatalysed reaction produced only traces of products. A number of points may be highlighted. The reaction is heterogeneous, since removal of catalyst during a reaction causes the reaction to stop; readdition of the catalyst causes the reaction to restart. All reactions with 3-buten-2-one proceed rapidly, and other electrophiles have typical relative reactivities. Catalyst reuse was studied in the reaction of **6** with **7**. Four reuses were possible, with the reaction time increasing on each reuse by ca. 20%. Ethyl cyanoacetate gives mono and dialkylated products. This is the only product detected in any of the reactions studied other than the desired mono-Michael adduct. No double Michael adducts are seen, a problem which is often encountered in these systems[9]. The reaction of ethyl cyanoacetate gives two diastereoisomers, as well as double product. The ratio of diastereoisomers varies between 13:1 and 10.4:1 depending on the ratio on reactants. This selectivity is occasionally seen in supported reagent catalysed reactions[10], but is absent in others[11,12].

The reactions of piperidine with various electrophiles were also studied. Only methyl methacrylate gave a slow enough uncatalysed reaction to make catalysis worthwhile. In this case good conversions were obtained, with reaction proceeding further at room temperature. Prolonged reaction times (up to 72 hours) failed to increase conversion. No reaction took place in toluene, in agreement with the earlier BINOLate work[5]. In keeping with the much lower reactivity of (meth)acrylates, only very low conversions were achieved with these electrophiles when C-centred nucleophiles were used.

Conclusions

Supported phenolates are very efficient and selective catalysts for the Michael reaction. The catalysts are simple to prepare and use. Products are formed rapidly under mild conditions in high yields. More resistant electrophiles such as (meth)acrylates are less susceptible to these catalysts.

Acknowledgements. DJM thanks the Royal Society for a University Research Fellowship.

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