Synthesis and olefination of carbonyl compounds using solid-supported reagents

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The development and application of three new solid-supported reagents for use in the synthesis or olefination of carbonyl compounds are described. The reagents include the Weinreb amide, Mukaiyama's *S*-2-pyridyl thioate and a Peterson methylenation reagent. As solid-supports *p*-benzyl alcohol resin, Wang resin and Merrifield resin (1–2% crosslinked polystyrene) have been used.

Introduction

Throughout the last decade, the pharmaceutical industry has gone through a major development which has resulted in an ever growing demand for faster formation of new, structurally diverse compounds. In the search for improved technologies for fast preparation of chemical libraries, a new variation of polymer-based synthesis has emerged. The method is termed polymer assisted solution-phase synthesis or synthesis using solid-supported reagents and catalysts. The technique relies on the addition of a polymer-bound reagent or catalyst to a substrate in solution in order to effect a chemical transformation. The product is isolated by simple filtration of the mixture and evaporation of the solvent. Since both substrate and product remain in solution during the reaction, it is possible to use traditional analytical techniques such as TLC, NMR and LCMS to monitor reaction progress.[1–3]

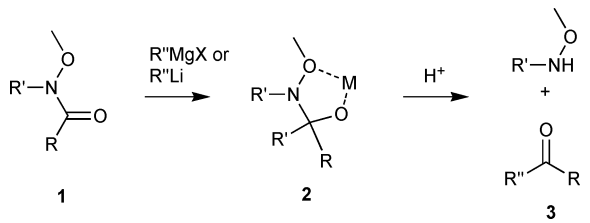
The methodology has found wide application over the last ten years, both in industry and in academic research groups. In particular the impressive achievements of the Ley group in preparing complex natural products exclusively by means of solid-supported reagents and catalysts have highlighted the versatility of this technique.[4–6]

Here we present the development and application of three new solid-supported reagents for use in the synthesis or olefination of carbonyl compounds. Carbonyl compounds and olefins are both important building blocks in organic synthesis, and an easy route to access these structures using solid-supported reagents would be of considerable synthetic interest. In the present work, the solid supports have been chosen based on which linker was suitable for attachment of starting materials.

Results and discussion

Weinreb amide

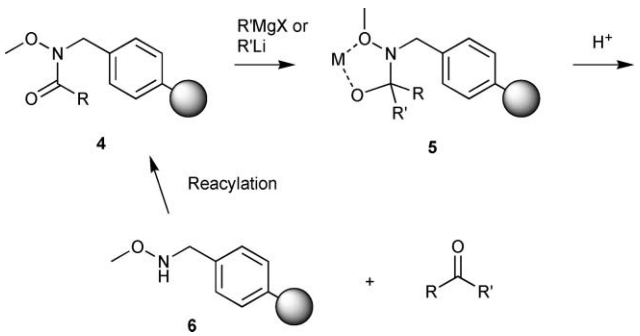
The Weinreb amide **1** (Scheme 1) constitutes one of the classical routes to carbonyl compounds through the combination of a carboxylic acid derivative and an organometallic reagent (Grignard, organolithium or DIBAL-H). Normally, no over-addition occurs due to formation of a stable chelated intermediate **2** which prevents further reaction with the organometallic reagent. Subsequent treatment with acid promotes decomposition of the intermediate to release the desired carbonyl compound **3**.[7–9] Since its discovery in the early eighties by Weinreb and co-workers, the method has found wide application in the synthesis of a variety of compounds.[10–12]



Scheme 1 Formation of carbonyl compounds using the Weinreb amide.

The feasibility of attaching a Weinreb amide to a solid support seems appealing, and with the increasing focus on solid-phase chemistry during the last decade, several examples of solid-supported Weinreb amides have appeared in the literature.[13–15]

We envisioned constructing a solid-supported Weinreb amide **4** (Scheme 2) that could be easily synthesized on a solid support and be regenerated by a simple acylation process and reused.



Scheme 2 Formation of carbonyl compounds using a solid-supported Weinreb amide.

Furthermore, we wanted to investigate other types of nucleophiles apart from the simple organometallic reagents that have

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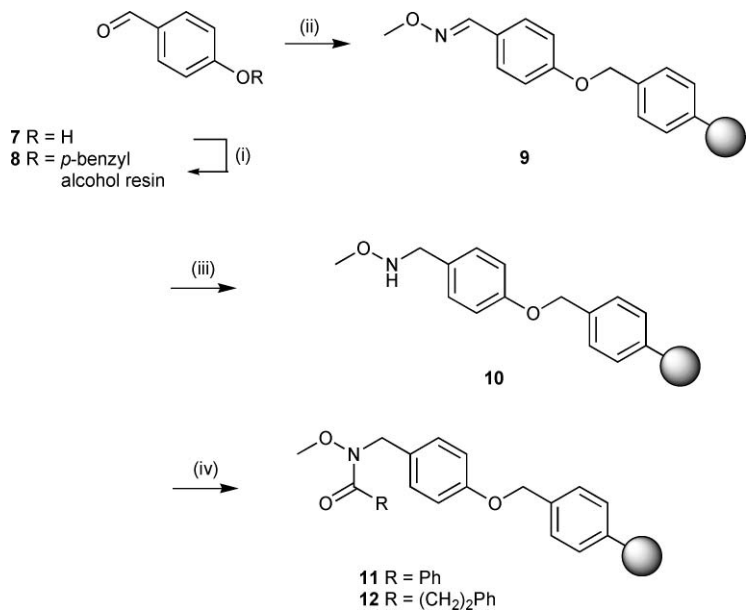


Scheme 3 *Reagents and conditions*: (i) *p*-benzyl alcohol resin, THF, PPh_3, DIAD, rt, 16 h, (ii) $MeONH_2HCl$, DIPEA, DMF, reflux, 8 h, (iii) $NaCNBH_3$, THF, H_2SO_4–MeOH, rt, 16 h, (iv) RCOCl, Et_3N, DCM, rt, 16 h.

already been reported, and to expand the range to include small heterocycles and alkynes containing an acidic hydrogen.

A solid-phase synthesis of the Weinreb amide was thus proposed (Scheme 3). *p*-Hydroxybenzaldehyde **7** was first attached to the polystyrene *via* a benzylalcohol linker under Mitsunobu conditions. The resulting resin **8** was next treated with *O*-methylhydroxylamine hydrochloride in the presence of DIPEA giving the oxime **9**. Reduction of **9** to the hydroxylamine was achieved by treatment with $NaCNBH_3$ in THF–MeOH in the presence of sulfuric acid, and finally acylation of amine **10** using benzoyl chloride or hydrocinnamoyl chloride in the presence of Et_3N completed the synthesis of the Weinreb reagents **11** and **12**.

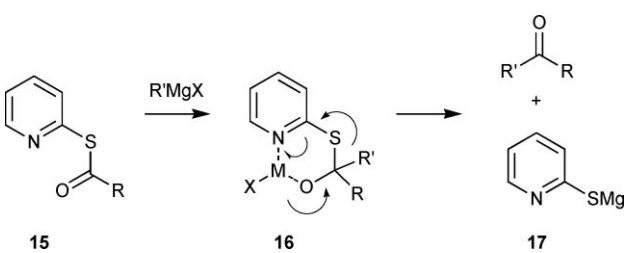
The solid-bound Weinreb reagents were first employed in the synthesis of carbonyl compounds using commercially available organometallic reagents (Table 1). The reactions were carried out at 0 °C in THF using a four fold excess of organometallic reagent. After stirring for one hour, a mixture of HCl (aq)–THF (1 : 1) was added whereby the carbonyl compound was liberated into solution. After filtration of the resin, the solvent was removed under reduced pressure and the crude product was passed through a short silica gel column.

No over-addition to give the tertiary alcohol was observed. We also tested lithiated alkynes and small heterocyclic compounds as nucleophiles (Table 1). The lithiation was carried out by treatment with an equivalent amount of *n*-BuLi in THF at 0 °C. After stirring for 30 min, the solution was transferred to the solid-supported Weinreb amide. Also in these cases no over-addition to give the tertiary alcohol was observed. After washing and drying, the spent resins **14** were reacylated and reused. Typically the yield of the carbonyl compound was unchanged after the first recyclization, hereafter it dropped with approximately 5% for each time the resin was recycled and the purity of the crude products was lower. It was possible to reuse a resin up to three times and still obtain an acceptable yield of carbonyl compound. The yields reported in Table 1 were obtained with a solid-bound Weinreb amide that had not been recycled.

The results obtained using simple organometallic reagents as nucleophiles are comparable to what has been reported by others.[13,14] To our knowledge there are no examples in the literature of using lithiated alkynes and heterocyclic compounds as nucleophiles in the reaction with solid-supported Weinreb amides. Nor are we aware of any examples of solid-supported Weinreb amides that have been recycled. The decrease in yields observed with recovered solids may be due to the low mechanical resistance of these solids under stirring, which gives rise to loss during filtration.

S-(2-Pyridyl) thioate

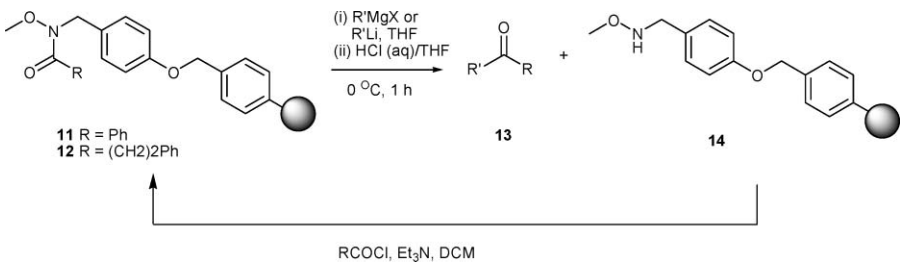
The formation of carbonyl compounds *via* addition of Grignard reagents to *S*-(2-pyridyl) thioates **15** (Scheme 4) was first reported by Mukaiyama and co-workers in 1973.[16,17] At that time the method proved to be superior over other known routes to carbonyl compounds such as addition of Grignard reagents to acid chlorides, amides or acid anhydrides, in that no formation of tertiary alcohols occurred. A mechanism was proposed by Mukaiyama as illustrated in Scheme 4.

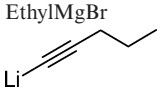
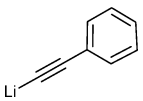


Scheme 4 Application of a solid-supported *S*-(2-pyridyl) thioate.

Upon addition of a Grignard reagent to the *S*-(2-pyridyl) thioate **15**, the 6-membered chelated intermediate **16** is formed

Table 1 Synthesis of carbonyl compounds using solid-supported Weinreb amide

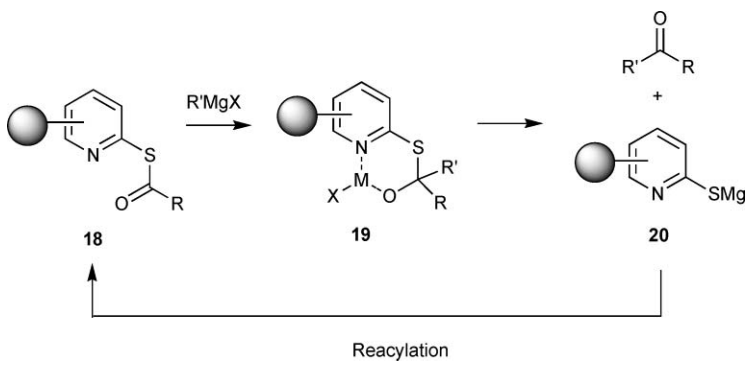


Entry	Nucleophile, R′	Yield (R = Ph)[a]	Yield (R = $(CH_2)_2Ph$)[a]
1	DIBAL-H	**13a** 27%	**13g** 24%
2	MeMgBr	**13b** 38%	**13h** 33%
3	PhMgBr	**13c** 37%	**13i** 38%
4	AllylMgBr	**13d** 35%	**13j** 30%
5	HexylMgBr	**13e** 35%	**13k** 27%
6	EthylMgBr	**13f** 32%	**13l** 29%
7		**13m** 35%	**13q** 31%
8		**13n** 25%	**13r** 23%
9		**13o** 34%	**13s** 33%
10		**13p** 36%	**13t** 33%

[a] The reported yields are based on the initial loading of the commercially available resin.

which initially was believed to be stable, thus preventing further addition of Grignard reagents. However, IR experiments during the reaction revealed the constant presence of a carbonyl stretch, indicating that the intermediate was not stable but immediately transformed to **17** and the carbonyl compound. It was hence concluded that the formation of carbonyl compounds could be attributed to the higher reactivity of the *S*-(2-pyridyl) thioates towards Grignard reagents compared to the ketone. This could be explained on the basis of a six-membered transition state in which the Grignard reagent is co-ordinated to the pyridyl nitrogen and the R′ group is transferred intramolecularly. Although not as common as the Weinreb amide, the above-described method has been applied in a number of synthetic transformations since it was first reported.[18–20] We were surprised that this useful technique has been under-used and the aim of our work was to develop a solid-supported version of the *S*-(2-pyridyl) thioate **18** (Scheme 5).

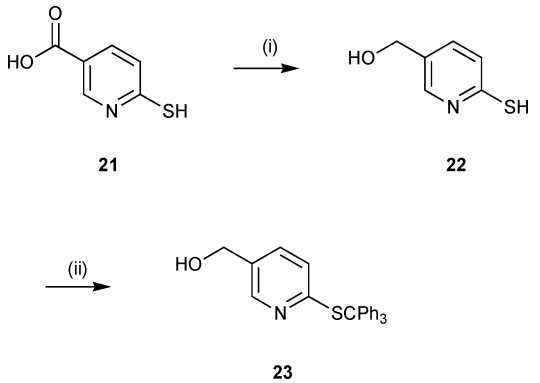
In contrast to the Weinreb amide, which forms a stable chelated intermediate, only an equivalent amount of Grignard reagent should be added to the *S*-(2-pyridyl) thioate. As for the solid-supported Weinreb amide we also wanted to investigate the



Scheme 5 Formation of carbonyl compounds using *S*-(2-pyridyl) thioate.

recovery and recycling of the spent solid-supported pyridine-2-thiol **20**.

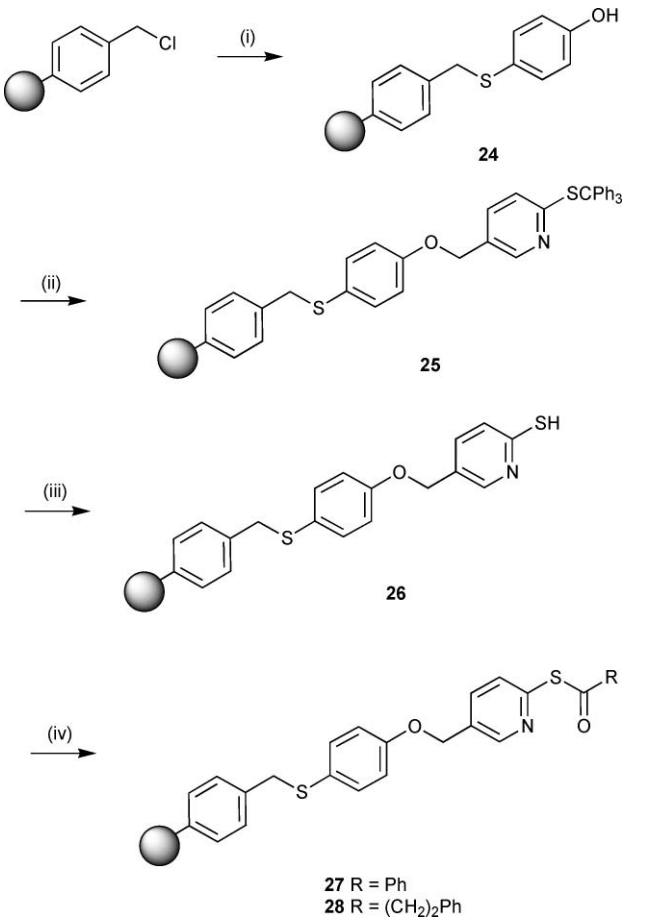
It was decided to focus on 6-mercaptonicotinic acid **21** as precursor for the reagent (Scheme 6).



Scheme 6 *Reagents and conditions*: (i) $LiAlH_4$, THF, 0 °C–rt, 16 h, 56%, (ii) $CClPh_3$, Et_3N, DCM–THF, 0 °C, 3 h, 83%.

Reduction of the carboxylic acid functionality using $LiAlH_4$ was accomplished in a moderate yield of 56%. Due to strong chelating abilities of compound **22**, extensive extraction with EtOAc–MeOH mixtures was necessary. A range of protecting groups was next tested for protection of sulfur. The protective group should be selectively introduced on sulfur in solution-phase and easily removed from the solid-supported compound and the trityl group turned out to be the best choice. Introduction was achieved by selective alkylation on sulfur using chlorotriphenylmethane in the presence of triethylamine in THF–DCM providing compound **23**.[21]

The synthesis of the solid-supported reagents was carried out as shown below (Scheme 7). Attachment of compound **23** to the linker **24** was achieved under Mitsunobu conditions.[22] Subsequent removal of the trityl group was performed by treatment with Et_3SiH–TFA in DCM.[23] Upon the deprotection, triphenylmethane was liberated to the solution as evident from TLC. The resulting resin **26**, which was now strongly yellow coloured, presumably due to the free mercapto group, was acylated employing triethylamine and benzoyl chloride or hydrocinnamoyl

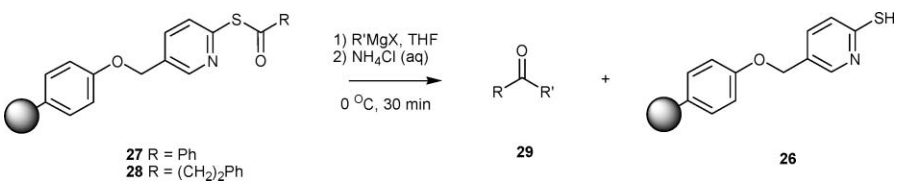


Scheme 7 *Reagents and conditions*: (i) KOH, DMF, 90 °C, 16 h, (ii) PPh_3, DIAD, **23**, rt, 14 h (iii) Et_3SiH–TFA–DCM (5 : 5 : 90), rt, 30 min, (iv) RCOCl, Et_3N, DCM, 0 °C, 3 h.

chloride in DCM providing resins **27** and **28**. During the acylation process partial disappearance of the yellow colour was observed.

By measuring the weight gain or loss after each transformation, the loadings were determined to 90–95% for all steps. Reagent **27** was next tested in the synthesis of carbonyl compounds (Table 2). Addition of phenylmagnesiumbromide (1 eqv.) in THF at 0 °C immediately liberated the corresponding carbonyl

Table 2 Addition of nucleophiles to solid-supported *S*-(2-pyridyl) thioate **27** and **28**



Entry	Nucleophile, R′	Yield (R = Ph)	Yield (R = $(CH_2)_2Ph$)
1	PhMgBr	70%	45%
2	DIBAL-H	No reaction	No reaction
3	EtMgBr	Over-addition	Over-addition
4	AllylMgBr	Over-addition	Over-addition

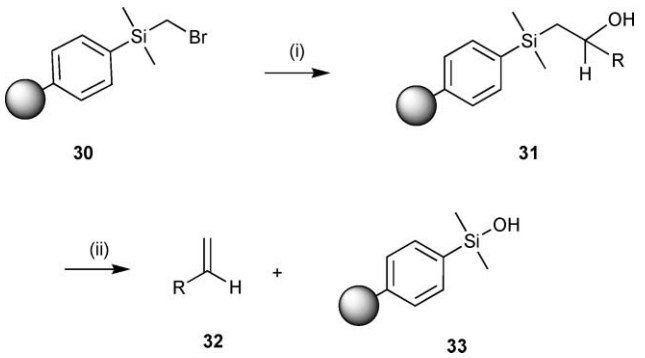
[a] The yields are based on the initial loading of the commercially available resin.

compound (benzophenone). The carbonyl compound was released after addition of only 0.5 eqv. of Grignard reagent without any acidic work-up. This observation verified Mukaiyama's proposed mechanism, which suggested that the chelated intermediate **16** (Scheme 4) was not stable but immediately decomposed to the carbonyl compound and the magnesium thiolate. During the reaction the resin stayed relatively colourless and only upon addition of water the strongly yellow colour appeared, presumably due to breakdown of the magnesium thiolate. Upon reaction of resin **28** with phenylmagnesiumbromide the corresponding carbonyl compound 1,3-diphenylpropan-1-one was obtained in 45% yield together with traces of the corresponding tertiary alcohol. After washing and drying, the spent resins **26** were reacylated, and reused in the synthesis of carbonyl compounds. An approximately 5% drop in the yields of carbonyl compounds (benzophenone and 1,3-diphenylpropan-1-one) after the second and third recycle was observed. Encouraged by these results we tested the addition of other nucleophiles to **27** and **28**.

Addition of DIBAL-H did not lead to any product formation (which was also the case in solution-phase experiments). Quite disappointingly, addition of either allylmagnesium-bromide or ethylmagnesiumbromide led to exclusive over-addition to give the tertiary alcohols even when only 0.5 eqv. of Grignard reagent were added (Table 2). We believe this is due to the decreased reactivity of the solid-bound *S*-(2-pyridyl) thioate reagent compared to the solution-phase analogue probably due to diffusion limitations, even though THF is a good solvent to swell the resin. As a result of this, the Grignard reagent is more prone to react with the already released carbonyl compound than the solid-supported *S*-(2-pyridyl) thioate reagent. That this does not seem to be the case in the formation of benzophenone is probably a result of both steric and electronic factors. (Solution-phase experiments using lithiated phenylacetylene, pentyne, furan and thiophene as nucleophiles (as described in Table 1 for the Weinreb amide) led to exclusive over-addition. Performing the reactions at low temperature (−78 °C) did not change the result.) Based on these results the method must therefore be considered to be limited to the synthesis of di-aryl ketone derivatives. Only an equivalent amount of organometallic reagent is allowed, which is naturally a limitation of the method. This can to some extent be compensated by the possibility to determine the loading of the resin relatively precisely, in that all the solid-phase transformations towards the reagent seem to proceed in almost quantitative yields. Moreover, the carbonyl compound is released and can be isolated prior to the aqueous work-up.

Methylenation using a solid-supported Peterson reagent

The Peterson olefination reaction is one of the most powerful routes to obtain olefins, and the method has been applied in the construction of a wide range of molecules.[24–26] We therefore wanted to investigate a solid-supported version of a Peterson methylenation reagent. The Peterson methylenation reaction has not found as wide an application in organic synthesis as for example the Wittig or Tebbe methylenation reactions, mainly due to the susceptibility of the silyllithium reagents to act as bases thus resulting in poor chemoselectivity. This can to some extent be overcome by concomitant treatment with ceriumtrichloride and TMEDA as described by Johnson and Tait.[27] Our approach to methylenation of carbonyl compounds using a solid-supported Peterson reagent was envisioned to proceed as shown below (Scheme 8).



Scheme 8 *Reagents and conditions*: (i) a) *n*-BuLi b) RCHO (ii) acid or base.

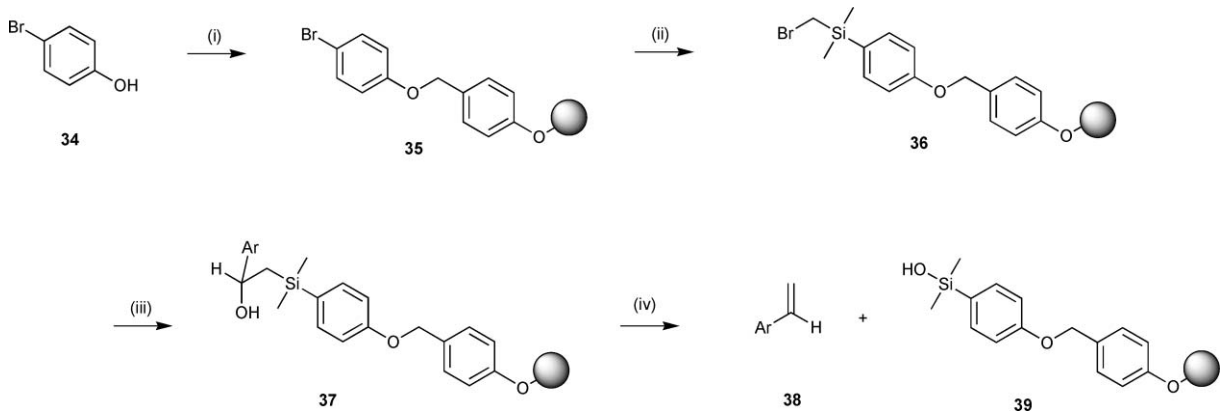
Halogen–lithium exchange of the solid-supported reagent **30** followed by addition of a carbonyl compound would generate the β-hydroxysilane **31**. Subsequent treatment with acid or base would liberate the olefin **32** into solution, leaving the silanol by-product **33** bound to the solid support which could then be removed by filtration. It was decided to focus on aromatic aldehydes as carbonyl compounds.

In order to form the solid-supported reagent, *p*-bromophenol **34** (Scheme 9) was first attached to the polystyrene using Mitsunobu conditions. The resulting solid-supported arylbromide **35** was treated with *n*-BuLi to effect the halogen–lithium exchange. Subsequent addition of (bromomethyl)dimethylsilylchloride provided compound **36** which was isolated by filtration and dried under reduced pressure.[28] Resin **36** was re-suspended in THF and treated with *n*-BuLi followed by addition of the aromatic aldehyde. After filtration and drying of the resulting β-hydroxysilane **37**, it was re-suspended in THF and treated with KO*t*Bu, whereby the olefin was released into solution.[29] The solid-supported silanol by-product was removed by filtration and the olefin isolated by evaporation of the solvent. A range of aromatic aldehydes with a diverse substitution pattern on the aromatic ring was tested in the methylenation reaction as shown in Table 3. The results clearly demonstrate the utility of the reagent in methylenation of aromatic aldehydes and to our knowledge this is the first example of a solid-supported Peterson reagent.

Conclusions

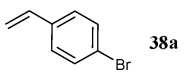
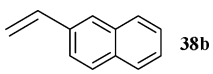
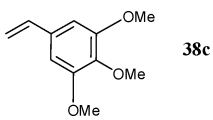
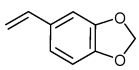
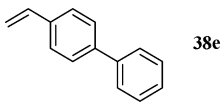
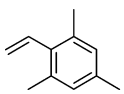
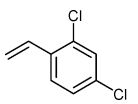
Two new solid-supported reagents have been developed and tested in the formation of carbonyl compounds, the Weinreb amide and the *S*-(2-pyridyl) thioate.

Addition of commercially available Grignard reagents or lithiated small heterocyclic compounds and alkynes to the solid-supported Weinreb amides gave the corresponding carbonyl compounds in good yields. Likewise, addition of phenylmagnesiumbromide to the solid-supported *S*-(2-pyridyl) thioates resulted in the corresponding carbonyl compounds. However, reaction with aliphatic Grignard reagents led to exclusive over-addition to give the tertiary alcohols. The method must therefore be considered to be limited to the synthesis of di-aryl ketone derivatives.



Scheme 9 *Reagents and conditions*: (i) Wang resin, PPh_3, DEAD, rt, 16 h, (ii) a) *n*-BuLi, THF, −78 °C, 2 h b) $BrCH_2(CH_3)_2SiCl$, THF, −78 °C–rt, 14 h, (iii) a) *n*-BuLi, THF, −78 °C, 2 h, b) RCHO, THF, 78 °C–rt, 14 h, (iv) KO*t*Bu, THF, 0 °C–rt, 16 h.

Table 3 Methylenation of aromatic aldehydes using a solid-supported Peterson reagent

Entry	Olefin	Yield[a]
1	 **38a**	25%[b]
2	 **38b**	30%
3	 **38c**	21%
4	 **38d**	18%
5	 **38e**	25%
6	 **38f**	22%
7	 **38g**	23%[b]

[a] The yields are based on the initial loading of the commercially available resin. [b] Due to volatility some material might have been lost during work-up.

Methylenation of aromatic aldehydes was achieved by means of a solid-supported Peterson reagent. A range of aldehydes with different substituents on the aromatic ring was tested. In all cases the methylenation reaction worked satisfactorily giving rise to the corresponding olefin products. For all reagents tested, the yields are lower than those obtained in solution, which in our experience is the norm for solid-supported reagents.

Experimental

General experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 Spectrometer or on a Varian Unity Inova 500 Spectrometer. Chemical shift values δ are reported in ppm relative to the residual undeuterated solvent signal as internal standard. IR spectra were recorded on a Perkin Elmer 1720 Infrared Fourier Transformer Spectrometer using KBr tablets. TLC was performed on 0.25 mm E. Merck silica gel plates (60F-274). The plates were visualized using ultraviolet light or by exposure to phosphomolybdic acid (10% in EtOH) followed by heating. Column chromatography was performed using Merck silica gel 60 with a particle size of 0.040–0.063. Melting points were obtained using a Heidolph capillary melting point apparatus and are uncorrected. HRMS was recorded at the Department of Chemistry, Copenhagen University.

THF was freshly distilled from sodium and benzophenone, DCM and Et_3N were freshly distilled from calcium hydride. DMF and MeOH were dried and stored over 4 Å molecular sieves. Other commercially available reagents were used without further purification unless otherwise noted.

Solid-supported reactions were carried out using a IKA KS 130 basic synthesizer. Solid-supported reactions under inert atmosphere or at low temperature were performed using standard glassware equipment and a magnetic stirrer bar. Resins were purchased from Nova Biochem or Aldrich. The loadings reported are based on the initial loading of the commercial resin and should be considered as approximations based on weight gain or loss of the resin after each chemical transformation. When several sequential synthetic steps were performed on solid phase the loadings are corrected for weight gain or loss of the resin.

Experimental procedures

Spectral and physical data for the following compounds are in accordance with those reported in the literature.

13a,[30] **13b**,[30] **13c**,[30] **13d**,[31] **13e**,[32] **13f**,[30] **13g**,[30] **13h**,[30] **13i**,[30] **13l**,[33] **13n**,[34] **13o**,[35] **13p**,[36] **13r**,[34] **13s**,[35] **13t**,[35] **38a**,[37] **38b**,[38] **38c**,[39] **38d**,[40] **38e**,[41] **38f**.[42]

Solid-supported 4-hydroxybenzaldehyde 8. *p*-Benzyl alcohol resin (1.2 mmol g^{-1}, 2.5 g, 3.0 mmol) was suspended in THF (25 ml) and *p*-hydroxybenzaldehyde (1.86 g, 15.0 mmol) and PPh_3 (3.93 g, 15.0 mmol) were added followed by DIAD (3.30, 2.8 ml, 15.0 mmol) in THF (2 ml). The mixture was agitated for 16 hours, filtered and washed with DCM (3 × 20 ml) and dried under reduced pressure. Loading: 95%; IR ν_{max}/cm^{-1} 1697 (CO).

Solid-supported (*E*)-benzaldehyde *O*-methyl oxime 9. Resin **8** (2.4 g, 2.51 mmol) was suspended in DMF (20 ml) and *O*-methylhydroxylamine hydrochloride (2.10 g, 25.1 mmol) and DIPEA (3.24 g, 4.30 ml, 25.1 mmol) were added. The mixture was heated at reflux for 8 hours. After cooling to room temperature the resin was filtered and washed with DMF (3 × 20 ml), THF–MeOH (1 : 1) (3 × 20 ml), THF (3 × 20 ml) and DCM (3 × 20 ml). The resin was dried overnight under reduced pressure.

Solid-supported 4-((methoxyamino)methyl)phenol 10. Resin **9** (2.4 g, 2.36 mmol) was suspended in THF (20 ml) and $NaCNBH_3$ (1.04 g, 16.5 mmol) was added. A mixture of MeOH–sulfuric acid (10 : 1) (5 ml) was added dropwise at 0 °C and the mixture was agitated for 16 hours at room temperature. The resin was filtered and washed with water–MeOH (1 : 1) (5 × 20 ml), THF–MeOH (1 : 1) (3 × 20 ml), THF (3 × 20 ml), and DCM (3 × 20 ml) and dried overnight under reduced pressure.

Solid-supported Weinreb amide, R = Ph 11, R = $(CH_2)_2$Ph 12. Resin **10** (2.0 g, 1.96 mmol) was suspended in dry DCM (20 ml) and Et_3N (1.39 g, 1.92 ml, 13.7 mmol) was added. The resin was agitated for 20 min followed by dropwise addition of the acid chloride (7 eqv.) in dry DCM (1 ml). After agitating for 16 h, the resin was washed with water–MeOH (1 : 1) (3 × 15 ml), THF–MeOH (1 : 1) (3 × 15 ml), THF (3 × 15 ml), and DCM (3 × 15 ml) and dried overnight under reduced pressure. Loading: 60% (over three steps); **11**: IR ν_{max}/cm^{-1} 1610 (CO); **12**: IR ν_{max}/cm^{-1} 1718 (CO).

General procedure for synthesis of carbonyl compounds using solid-supported Weinreb amides 11 and 12. To an ice-cooled suspension of the solid-bound Weinreb amides **11** (0.5 g, 0.43 mmol) or **12** (0.5 g, 0.41 mmol) in dry THF (5 ml), was added the nucleophilic reagent (4 eqv.) dropwise under argon. After agitating for one hour, HCl (aq) (1M)–THF (1 : 1) (2 ml) was added slowly. The mixture was agitated for an additional 15 min, filtered and washed with THF (3 × 5 ml) and DCM (3 × 5 ml). The filtrate was evaporated to dryness, dissolved in EtOAc–hexane (1 : 1) and passed through a short silica gel column. The solvent was removed under reduced pressure and the product was dried overnight.

General procedure for preparation of lithiated nucleophiles

The substrate was dissolved in dry THF at 0 °C under argon and *n*-BuLi (1 eqv.) was added dropwise. The mixture was stirred at 0 °C for 30 min and then added dropwise to the solid-bound Weinreb amide.

General procedure for reacylation of used resin 14. The spent resin was washed with water–MeOH (1 : 1) (3 × 5 ml), MeOH (3 × 5 ml), THF (3 × 5 ml), and DCM (3 × 5 ml) and dried overnight under reduced pressure. Dry DCM (5 ml) was added to the resin followed by Et_3N (7 eqv.). After 30 min, the acid chloride (7 eqv.) in DCM (1 ml) was added dropwise, and the mixture was agitated for 16 hours. The resin was filtered and washed with THF–MeOH (1 : 1) (3 × 10 ml), THF (3 × 10 ml) and DCM (3 × 10 ml) and dried overnight under reduced pressure.

1-Phenylhex-2-yn-1-one 13m. Compound **13m** (26 mg, 0.15 mmol, 35%) was prepared following the general procedure. δ_H (300 MHz, $CDCl_3$) 8.15 (2 H, d, *J* 8.0), 7.58 (1 H, m), 7.45 (2 H, m), 2.45 (2 H, t, *J* 7.2), 1.67 (2 H, tq, *J* 7.2, 7.0), 1.05 (3 H, t, *J* 7.1); δ_C (75 MHz, $CDCl_3$) 178.2, 136.8, 133.9, 129.5, 128.4, 96.7, 79.7, 21.3, 21.1, 13.6; *m/z* (+FAB) 173.0966 (M + H^+). $C_{12}H_{12}O$ requires 172.0888.

1-Phenylhex-5-en-3-one 13j. Compound **13j** (21 mg, 0.12 mmol, 30%) was prepared following the general procedure. δ_H (300 MHz, $CDCl_3$) 7.15–7.37 (5 H, m), 5.90 (1 H, m), 5.15 (1 H, m), 5.11 (1 H, m), 3.17 (2 H, m), 2.92 (2 H, t, *J* 6.9), 2.75 (2 H, t, *J* 6.9); δ_C (75 MHz, $CDCl_3$) 193.2, 140.9, 130.0, 128.4, 128.3, 126.1, 118.9, 47.8, 43.8, 29.6; *m/z* (+FAB) 175.1121 (M + H^+). $C_{12}H_{14}O$ requires 175.1123.

1-Phenylnonan-3-one 13k. Compound **13k** (24 mg, 0.11 mmol, 27%) was prepared following the general procedure. δ_H (300 MHz, $CDCl_3$) 7.31 (2 H, m), 7.18 (3 H, m), 2.91 (2 H, t, *J* 7.2), 2.71 (2 H, t, *J* 7.2), 2.35 (2 H, t, *J* 7.1), 1.53 (2 H, m), 1.27 (6 H, m), 0.88 (3 H, t, *J* 7.1); δ_C (75 MHz, $CDCl_3$) 210.4, 141.1, 128.4, 128.3, 126.0, 44.2, 43.0, 31.5, 29.7, 28.8, 23.7, 22.4, 14.0; *m/z* (+FAB) 241.1568 (M + Na^+). $C_{15}H_{22}O$ requires 241.1568.

1-Phenyloct-4-yn-3-one 13q. Compound **13q** (22 mg, 0.13 mmol, 31%) was prepared following the general procedure. δ_H (300 MHz, $CDCl_3$) 7.25 (2 H, m), 7.08–7.12 (3 H, m), 2.90 (2 H, t, *J* 7.0), 2.75 (2 H, t, *J* 7.0), 2.10 (2 H, t, *J* 6.9), 1.55 (2 H, tq, *J* 7.0, 7.0), 0.93 (3 H, t, *J* 7.0); δ_C (75 MHz, $CDCl_3$) 187.8, 140.7, 128.6, 127.5, 126.3, 98.6, 91.9, 43.8, 32.7, 21.3, 20.3, 13.5; *m/z* (+FAB) 223.1106 (M + Na^+). $C_{14}H_{16}O$ requires 223.1099.

6-(Mercaptopyridine-3-yl)methanol 22. To an ice-cooled solution of $LiAlH_4$ (1 M in THF, 58 mmol, 58.0 ml) in dry THF (200 ml) was added 6-mercaptonicotinic acid (6.0 g, 38.8 mmol) in small portions. After stirring for 16 hours, the mixture was cooled to 0 °C and cold water (2.4 ml) was added slowly followed by NaOH (aq) (4 M, 2.4 ml) and additional cold water (6.8 ml). The mixture was filtered and the solid was extracted repeatedly with a mixture of EtOAc–MeOH 9 : 1. The filtrate was concentrated under reduced pressure and purified by column chromatography (eluent: EtOAc–MeOH 9 : 1) to give compound **22** (3.06 g, 21.6 mmol, 56%) as a yellow solid. Mp.: 85–87 °C; δ_H (300 MHz, $CDCl_3$) 7.98 (1 H, s), 7.75 (1 H, m), 7.61 (1 H, m), 4.68 (2 H, s); δ_C (75 MHz, $CDCl_3$) 176.8, 137.8, 136.0, 133.2, 128.1, 60.1; *m/z* (+EI) 141.

(6-Tritylthio)pyridine-3-yl)methanol 23. Compound **22** (6.0 g, 42.6 mmol) was dissolved in dry DCM–dry THF (1 : 1) (150 ml) and Et_3N (8.60 g, 11.8 ml, 85.1 mmol) was added. The solution was cooled to 0 °C and triphenylchloromethane (13.05 g, 46.8 mmol) in dry THF (60 ml) was added slowly. After stirring for 3 hours, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ (aq) (2 × 100 ml) and saturated NaCl (aq) (2 × 100 ml). The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and the crude product was purified by column chromatography (eluent: hexane–EtOAc 8 : 1 to 2 : 1) to give compound **23** (13.5 g,

35.3 mmol, 83%) as a light yellow solid. Mp.: 137–140 °C; δ_H (300 MHz, $CDCl_3$) 8.22 (1 H, s), 7.43 (6 H, m), 7.23 (10 H, m), 6.60 (1 H, d, *J* 8.1), 4.51 (2 H, s), 2.67 (1 H, s); δ_C (75 MHz, $CDCl_3$) 158.4, 147.5, 143.9, 134.9, 132.9, 130.0, 127.9, 127.0, 124.9, 70.3, 62.1; *m/z* (+FAB) 384.1422 ($M + H^+$). $C_{25}H_{22}NOS$ requires 384.1422.

Solid-supported *p*-mercaptophenol 24. To a suspension of Merrifield resin (1.0 mmol g^{-1}, 3.0 g, 3.0 mmol) in dry DMF (30 ml) was added KOH (1.65 g, 30 mmol) and *p*-mercaptophenol (1.89 g, 15 mmol). The mixture was heated at 90 °C for 16 hours. After cooling to room temperature the resin was filtered and washed with water–MeOH (1 : 1) (3 × 25 ml), DMF (3 × 25 ml), MeOH (3 × 25 ml), THF (3 × 25 ml) and DCM (3 × 25 ml). The resin was dried under reduced pressure overnight. Loading: 93%.

Solid-supported (6-(tritylthio)pyridin-3-yl)methanol 25. Resin **24** (2.5 g, 2.27 mmol) was suspended in THF (20 ml) and PPh_3 (2.38 g, 9.1 mmol) and compound **23** (3.49 g, 9.1 mmol) was added. DIAD (1.84 g, 1.79 ml, 9.1 mmol) in THF (2 ml) was added dropwise and the resin was agitated for 14 hours, filtered and washed with MeOH (3 × 20 ml), THF (3 × 20 ml) and DCM (3 × 20 ml) and dried under reduced pressure overnight. Loading: 97%.

Solid-supported (6-mercaptopyridine-3-yl)methanol 26. Resin **25** (3.0 g, 1.63 mmol) was treated with a mixture of TFA–Et_3SiH–DCM (5 : 5 : 90) (20 ml) for 15 minutes. After filtration of the resin, the procedure was repeated. The resin was washed with MeOH–THF (1 : 1) (3 × 20 ml), THF (3 × 20 ml), DCM (3 × 20 ml) and dried under reduced pressure. Loading: 96%.

Solid-supported *S*-(2-pyridyl) thioate (mercaptophenol linker), R = Ph 27 R = $(CH_2)_2$Ph 28. Dry DCM (10 ml) was added to resin **26** (1.0 g, 0.8 mmol) at 0 °C followed by Et_3N (5 eqv.). After 45 minutes the acid chloride (5 eqv.) in dry DCM (1 ml) was added dropwise. The resin was agitated for 3 hours at 0 °C, filtered and washed with MeOH–water (1 : 1) (3 × 10 ml), MeOH (3 × 10 ml), MeOH–THF (1 : 1) (3 × 10 ml), THF (3 × 10 ml), DCM (3 × 10 ml). The resin was dried under reduced pressure. Loading **27**: 95%, **28**: 90%.

General procedure for solid-phase synthesis of carbonyl compounds using *S*-(2-pyridyl) thioate resins 27 and 28. Dry THF (3 ml) was added to the resin **27** (0.5 g, 0.34 mmol) or resin **28** (0.5 g, 0.33 mmol) under argon at 0 °C followed by dropwise addition of the organometallic reagent (1 eqv.) The mixture was stirred at 0 °C for 30 min followed by slow addition of saturated NH_4Cl (aq) (2 ml) and water (1 ml). The resin was stirred for 15 min, filtered and washed with THF (5 × 5 ml). The filtrate was concentrated under reduced pressure, dissolved in EtOAc–hexane (1 : 1), passed through a short silica gel column and concentrated under reduced pressure. Alternatively, the carbonyl compound could be isolated by filtration of the resin prior to the aqueous work-up. Saturated NH_4Cl (aq) should then be added to the resin afterwards to break down the magnesium thiolate.

General procedure for reacylation of used resin 29. The spent resin **29** was washed with water–MeOH (1 : 1) (3 × 5 ml), MeOH (3 × 5 ml), THF (3 × 5 ml) and DCM (3 × 5 ml) and dried overnight under reduced pressure. Dry DCM (5 ml) was added to the resin followed by Et_3N (5 eqv.) and the mixture was cooled to 0 °C. After 45 min, the acid chloride (5 eqv.) in DCM (1 ml) was added dropwise, and the mixture was agitated for 3 hours. The resin was filtered and washed with THF–MeOH (1 : 1) (3 × 10 ml), THF (3 × 10 ml) and DCM (3 × 10 ml) and dried overnight under reduced pressure.

Solid-supported 4-bromophenol 35. Wang resin (1.2 mmol g^{-1}, 3.0 g, 3.6 mmol) was suspended in dry THF (30 ml) and *p*-bromophenol (2.49 g, 14.4 mmol) and PPh_3 (3.77 g, 14.4 mmol) were added, followed by DEAD (2.51 g, 2.34 ml, 14.4 mmol) in THF (1 ml) dropwise. The mixture was agitated for 16 hours, filtered and washed with THF–MeOH (1 : 1) (3 × 20 ml), THF (3 × 20 ml) and DCM (3 × 20 ml). The resin was dried under reduced pressure overnight. Loading: 96%.

Solid-supported 4-((bromomethyl)dimethylsilyl)phenol 36. Resin **35** (3.0 g, 2.92 mmol) was suspended in dry THF (25 ml) under argon and cooled to −78 °C. *n*-BuLi (1.6 M in hexane, 5.48 ml, 8.76 mmol) was added dropwise and stirring was continued for 2 hours at −78 °C. The resin was washed under argon with dry THF (3 × 20 ml) and re-suspended in dry THF (20 ml). (Bromomethyl)dimethylchlorosilane (2.74 g, 1.98 ml, 14.6 mmol) in dry THF (1 ml) was added dropwise at −78 °C and the mixture was stirred for 5 hours and then quenched by addition of saturated NH_4Cl (aq) (3 ml). After warming to room temperature the resin was filtered and washed with H_2O–THF (1 : 1) (5 × 20 ml), THF (5 × 20 ml) and DCM (3 × 20 ml) and dried under reduced pressure overnight.

General procedure for methylenation of aromatic aldehydes using resin 36. *n*-BuLi (3 eqv.) was added dropwise to a suspension of resin **36** (0.5 g, 0.44 mmol) in THF (5 ml) at −78 °C under argon. After stirring for two hours, the aldehyde (5 eqv.) in THF (0.5 ml) was added dropwise and stirring was continued for 3 hours at −78 °C. The mixture was allowed to warm to room temperature overnight, water (2 ml) was added slowly and the resin was filtered and washed with THF–water (1 : 1) (3 × 5 ml), THF (3 × 5 ml), DCM (3 × 5 ml) and THF (3 × 5 ml). After drying, the resin was re-suspended in dry THF (5 ml) under argon and KO*t*Bu (3 eqv.) was added at 0 °C. The mixture was allowed to warm to room temperature overnight, filtered and washed with THF (3 × 5 ml) and DCM (3 × 5 ml). The solvent was removed *in vacuo* and the crude olefin was dissolved in pentane–EtOAc (4 : 1), passed through a short silica gel column (eluent: pentane) and concentrated under reduced pressure.

2,4-Dichloro-1-vinylbenzene 38g. Compound **38g** (17 mg, 0.1 mmol, 23%) was prepared following the general procedure. δ_H (300 MHz, $CDCl_3$) 7.48 (1 H, m), 7.38 (1 H, m), 7.20 (1 H, m), 7.02 (1 H, dd, *J* 17.8, 11.6), 5.72 (1 H, dd, *J* 17.8, 1.1), 5.40 (1 H, dd, *J* 11.6, 1.1); δ_C (75 MHz, $CDCl_3$) 134.2, 133.8, 133.6, 132.1, 129.3, 127.3, 127.2, 117.0; *m/z* (+FAB) 171.9754 (M^+). $C_8H_6Cl_2$ requires 171.9847.

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