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Enamines in solid-phase: synthesis and reactivity towards electrophiles[†]

Fernando Aznar,* Carlos Valdés and María-Paz Cabal

Instituto de Química Organometálica 'Enrique Moles', Unidad Asociada al CSIC, Universidad de Oviedo, Oviedo 33071, Spain

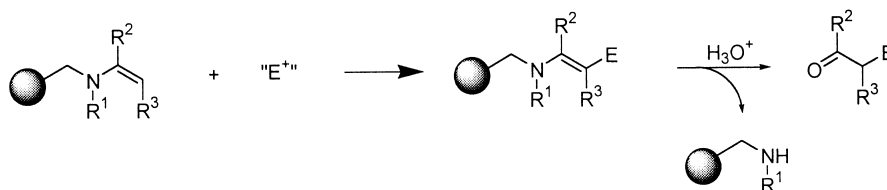
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Abstract

Enamines are synthesized in solid-phase by amination of terminal acetylenes with a secondary amine attached to Wang resin in a process catalyzed by mercury(II) acetate. The enamines obtained react with electrophiles such as isocyanates and nitroolefins to give rise to the expected addition products, which can be released from the resin by hydrolysis of the enamine under mild acidic conditions. © 2000 Elsevier Science Ltd. All rights reserved.

The development of combinatorial chemistry as a tool for the discovery of new drugs and biologically active molecules has promoted a spectacular growth in solid-phase organic synthesis.¹ Nowadays, solid-phase chemistry² is not restricted to the classic peptide couplings, but in fact has been extended to carbon–carbon bond-forming processes, such as olefination reactions, organometallic carbon–carbon couplings or ring closing metathesis.³

Nevertheless, many reactions and synthetic strategies that are commonly done in solution phase have yet to be applied to solid-phase synthesis. One typical example is the addition of an enamine to a carbon electrophile, such as a carbonyl compound, an acylating agent, a nitroolefin, which is a well documented method for the creation of carbon–carbon bonds in solution,⁴ and could be an excellent starting point for the synthesis of libraries of organic compounds in solid-phase. Moreover, by attaching the enamine to the resin via the amino group, the final compound could be cleanly released from the resin by treatment under mild acidic conditions to yield the free compound having a ketone functionality (Scheme 1).



Scheme 1.

* Corresponding author. Tel: (34)985103454; fax: (34)985103446; e-mail: fag@sauron.quimica.uniovi.es

[†] Dedicated to Prof. José Barluenga on the occasion of his 60th Birthday.

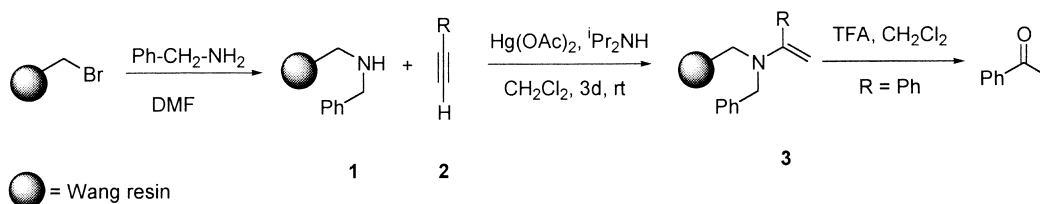
In contrast to the wide spread use of imines in solid-phase organic synthesis,⁵ to the best of our knowledge, the only example of an enamine used in solid-phase organic chemistry was disclosed by Hird et al. for 2-amino-1,3-dienes and their cycloaddition reactions.⁶ A possible explanation could be the lack of a synthetic method for the synthesis of enamines that can be easily adapted to solid-phase chemistry.

Enamines formally derived from methyl ketones can be easily prepared by the addition of secondary amines to terminal acetylenes, in a process catalyzed by mercury salts.⁷ The usefulness of this methodology has been explored in our group for the synthesis of 2-amino-1,3-butadienes from conjugated enynes,⁸ and their synthetic applications in cycloaddition reactions.⁹

In this paper we describe the application of this methodology to the solid-phase synthesis of enamines, and their subsequent reactions with selected electrophiles.

1. Results and discussion

We carried out our studies with the solid-supported amine **1**, that is readily prepared by reaction of 4-(bromomethyl)phenoxymethyl polystyrene (Wang Bromo polystyrene resin) and benzylamine. In the initial experiments with phenylacetylene ($R = \text{Ph}$), the amination reaction proceeded by treating the resin in CH_2Cl_2 , with a solution of phenylacetylene, $\text{Hg}(\text{OAc})_2$ and diisopropyl amine in CH_2Cl_2 . Best results were obtained after 72 hours at room temperature. At this point, treatment of the resin with a 10% trifluoroacetic acid solution in CH_2Cl_2 afforded acetophenone, providing evidence of the formation of enamine **3** (Scheme 2).

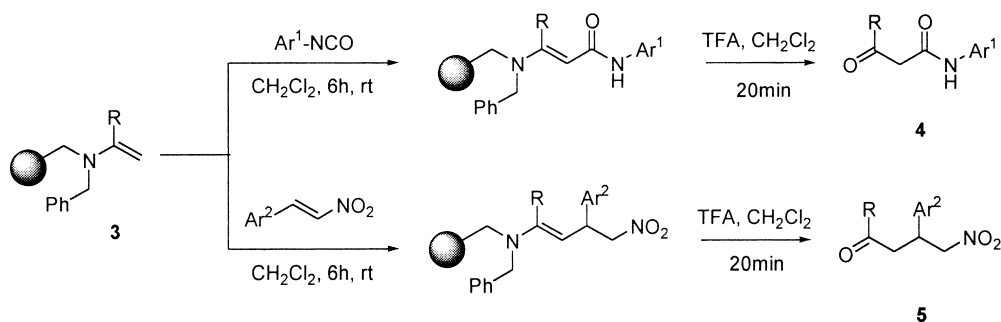


Scheme 2.

In order to study the scope of this reaction we tried different terminal acetylenes. This time, we did not isolate the corresponding methyl ketones, but instead we allowed resin **3** to react with electrophiles. Thus, reaction of the enamine resin **3** with an aromatic isocyanide in CH_2Cl_2 followed by treatment with 5% TFA in wet CH_2Cl_2 provides ketoamide **4**. Similarly, reaction of the enamine resin **3** with nitroolefins gives rise after the hydrolytic cleavage under the same conditions to nitroketones **5** (Scheme 3, Table 1).

In both types of reactions the purities and overall yields of the processes range from moderate to good (in some instances a small amount of methyl ketone was detected by ^1H NMR). The methodology appears to be applicable to neutral and electron rich aromatic acetylenes and conjugated enynes[‡] (**4g–i**). However, no reaction product is isolated for aromatic acetylenes with

[‡] The reaction of 2-amino-1,3-butadienes with nitroolefins was not attempted since it is well known that it affords a mixture of cyclic and open chain compounds both in solution and in solid-phase.⁶



Scheme 3.

Table 1
 β -Ketoamides **4** and γ -nitroketones **5** prepared^a

Compound	R	Ar ¹	Ar ²	Yield ^b (%)	Purity ^c (%)
4a	Ph	Ph		63	81
4b	Ph	<i>p</i> -Tolyl		72	86
4c	<i>p</i> -Tolyl	Ph		67	91
4d	<i>m</i> -MeO-Ph	Ph		51	88
4e	<i>p</i> -MeO-Ph	<i>p</i> -Tolyl		68	90
4f	<i>p</i> -Ph-Ph ^d	Ph		45	-
4g	1-Cyclopentenyl	Ph		67	65
4h	1-Cyclohexenyl	Ph		77	79
4i	1-Cyclohexenyl	<i>p</i> -Tolyl		60	74
5a	Ph		Ph	49	90
5b	Ph		2-Furyl	87	78
5c	Ph		<i>p</i> -MeO-Ph	51	81
5d	<i>p</i> -Tolyl		Ph	57	87
5e	<i>p</i> -MeO-Ph		2-Furyl	52	84
5f	<i>p</i> -MeO-Ph		<i>p</i> -MeO-Ph	54	89
5g	<i>p</i> -Cl-Ph		Ph	52	71
5h	<i>p</i> -(CH ₃ CO)-Ph		Ph	0	-
5i	<i>p</i> -NO ₂ -Ph		Ph	0	-
5j	CH ₃ -(CH ₂) ₄ -		Ph	0	-

^a All compounds gave satisfactory NMR and MS spectra. ^b Yield based on weight of crude extract from the resin and calculated from the theoretical loading of commercial Bromo-Wang resin. ^c Purity was determined by analytical HPLC, by comparison with an analytically pure sample of the same compound. ^d The amination reaction was carried out in THF instead of CH₂Cl₂.

electron withdrawing substituents (**5h,i**) and alkylsubstituted acetylenes (**5j**). In some examples the insolubility of the intermediates gives rise to the final compound with low yield and purity (**4f**).

In conclusion, we have presented a new method for the synthesis of enamines in solid-phase, and some examples of their reactivity with typical electrophiles. Given the variety of electrophiles that can react with enamines and the ready availability of aromatic acetylenes by Sonogashira coupling¹⁰ or Corey–Fuchs reaction,¹¹ we believe this method can be very useful as a starting point for the preparation of libraries of organic compounds.

2. Experimental procedure

2.1. Preparation of aminobenzyl Wang resin **1**

To a suspension of commercial 4-(bromomethyl)phenoxyethyl polystyrene (loading 0.8–1.4 mMol/g) (4 mMol) in 25 mL of DMF was added benzylamine (20 mMol, 2.14 g) and the mixture was shaken overnight. The solvent was removed by filtration and the resin was washed with DMF (3×50 mL) and CH₂Cl₂ (3×50 mL) and dried under vacuum. Then the resin was transferred to a round-bottomed flask and swollen with 50 mL of benzene, the suspension was refluxed overnight with a Dean–Stark apparatus and a reflux condenser, in order to remove any traces of water. The solvent was removed by filtration and the resin was dried under vacuum and stored in a desiccator.

2.2. General procedure for the solid-phase synthesis of amides **4** and nitro derivatives **5**

1. *Amination reaction*: To a suspension of mercury(II) acetate (180 mg, 0.6 mMol) in 3 mL of dry THF was added the terminal acetylene (0.7 mMol) and the mixture was stirred for 10 min. Then 0.24 mL (1.8 mMol) of dry diisopropyl amine was added and the stirring continued for 15 min. The solution was transferred to a suspension of aminobenzyl Wang resin **1** (0.2 mMol) in 2 mL of dry CH₂Cl₂. The mixture was shaken for 72 h at room temperature. The solution was removed by filtration, and the resin was washed once with 10 mL of dry CH₂Cl₂.

2. *Addition of the electrophile and hydrolysis of the enamine—synthesis of compounds **4** and **5***: To the resin swollen in 3 mL of dry CH₂Cl₂ was added a solution of the electrophile (1.8 mMol) in 3 mL of CH₂Cl₂. The mixture was shaken for 6 h and then the solution was removed from the resin by filtration. The resin was washed with CH₂Cl₂ (3×15 mL), THF (3×15 mL), MeOH (2×10 mL) and CH₂Cl₂ (15 mL). A 10% solution of TFA in CH₂Cl₂ was added to the resulting resin and the mixture was shaken for 20 min. The solution was filtered and the resin was washed with additional CH₂Cl₂. The filtrates were combined and evaporated under reduced pressure. The residue was treated with 4 mL of CH₂Cl₂ and charcoal and the solution was filtered through Celite and concentrated under reduced pressure to afford either compound **4** or **5**.

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