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Tetrahedron Letters 45 (2004) 243–248

Tetrahedron Letters

Gallium metal mediated allylation of carbonyl compounds and imines under solvent-free conditions

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Received 25 September 2003; revised 22 October 2003; accepted 30 October 2003

Abstract—Gallium metal is effective in mediating the allylation of various carbonyl compounds and imines under solvent-free conditions, with the application of sonic energy, affording the corresponding homoallylic alcohols and amines. The imines themselves were also prepared under solventless conditions in high yield, thereby establishing a two-step solvent-free synthesis of homoallylic amines. In comparison, indium metal produced a mixture of the desired homoallylic secondary amine and the bis-allylated species via an iminium ion intermediate.

1. Introduction

We have recently established that homoallylic alcohols can be readily prepared from carbonyl compounds and allylic halides under metal mediated solvent-free conditions using In, Bi, Zn[1] and Sn[2] in Barbier–Grignard type reactions. This is an important addition to the variety of procedures which utilise benign reaction media, such as water and ionic liquids. From a green perspective, the solvent-free alternative alleviates entirely the need to dispose of, or recycle, the reaction media. Furthermore, the use of water as a reaction media for such 1,2-additions inhibits the scope of the reaction to only hydrolytically robust substrates such as carbonyl compounds, thus excluding compounds such as most imines.[3]

The 1,2-addition of organometallic reagents to imines is an established route to homoallylic amines, which are important fundamental building blocks in many biologically active compounds.[4] The traditional synthetic procedures for their synthesis involve the exclusion of air and moisture, the use of dry solvents and highly reactive organometallic reagents, mostly allylic compounds of Li, Mg, Cu and Zn.[5] Though much attention has been given to the production of benign synthetic protocols for the allylation of carbonyl compounds,[6] the allylation of imines has been somewhat neglected. The contributing factors to this include: the low reactivity of unactivated imines towards nucleophilic addition, their tendency to deprotonate when they are derived from enolisable carbonyl compounds and their sensitivity to water.[4] Given these properties (particularly their hydrolytic instability), solvent-free approaches to the synthesis of allylated amines are attractive in providing such compounds, and the drive towards the development of more benign synthetic protocols.

In extending our previous investigations, we now focus on the potential use of gallium metal in solvent-free allylation reactions. Gallium is of particular interest for several reasons over and above the fact that in comparison with the other group 13 elements its role as a potential mediator in organometallic reactions has been largely ignored.[7] Its low first ionisation potential of 5.99 eV (cf. Li 5.39, Mg 7.65 eV) makes it useful for single electron transfer reactions, which combined with its low vapour pressure and the fact it is liquid at low temperatures (mp 29.8 °C), makes it an attractive candidate for metal mediated reactions.[8] Furthermore, commercially available metallic Ga 99.99% is a relatively inexpensive metal.[9] However, as with the imines themselves, the organometallic complexes of Ga can be unstable to water leading to a significant reduction in reactivity through hydroxide and galloxane formation,[10] although the

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Keywords: Gallium; Indium; Imines; Allylation; Solvent free; Aldehydes.

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0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.188

possible catalytic role of these compounds should not be ignored. Furthermore, we have investigated the use of both indium and gallium metal in the solvent-free allylation of imines to assess whether protocols developed for the allylation of carbonyl compounds could be extended to imines. The imines we have investigated were also prepared under solvent-free conditions via condensation reactions of aldehydes with aniline, thereby establishing a completely solvent-free synthetic protocol for the synthesis of homoallylic amines.

2. Synthesis of homoallylic alcohols

We first investigated the allylation of carbonyl compounds using gallium metal with the aim of establishing its suitability for the allylation of imines and to compare it with indium as a mediator in such reactions. A typical experiment involved the addition of allyl bromide (7.25 mmol) to a mixture of commercially available gallium metal (5 mmol) and a carbonyl compound (5 mmol) under an inert atmosphere of nitrogen. The mixture was sonicated for 12 h, before quenching with water (ca. 0.5 mL) and extraction of the alcohol into diethyl ether, Scheme 1. The resulting alcohol was then purified by flash chromatography (10:1 hexane–ethyl acetate) mixture.

Under sonication the reactions proceeded smoothly and efficiently with yields ranging from 74% to 97%, Table 1, for aromatic, –OMe substituted aromatic and aliphatic aldehydes. However, the system was not effective with ketones or hydroxybenzaldehydes. With the exception of the hydroxybenzaldehydes the addition reactions gave comparable yields to those obtained when using indium metal in previous solvent-free reactions.[1] In contrast, in the absence of sonication and with the reaction mixtures simply agitated by stirring, only relatively low yields were obtained. Given the similar first ionisation potentials (IP) of indium, 5.70 eV, and gallium, 5.99 eV, and the liquid state of gallium just above room temperature, it was surprising that gallium required sonication whilst for indium simply stirring was effective. This raises the issue of whether sonication for gallium is required to clean the metal surface, or whether sonication influences the chemical reactivity of the gallium metal. Accordingly, we carried out the reaction of benzaldehyde in the absence of sonication at 35 °C (above the melting point of the metal), whereby clean metal surface should constantly be available for the reactive substrate. However, this resulted in a very low yield of homoallylic alcohol on work-up, though a complication may be loss of the allyl bromide from the reaction mixture at elevated temperatures. In turning to a less volatile substrate, the reaction of crotyl bromide was investigated, resulting in a high yield of the homoallylic alcohol (γ-allylation product), ca. 94%, which is comparable to that obtained on sonication of the reaction mixture, ca. 91%. Therefore, it can be inferred that while the role of sonication is important when using highly volatile allyl bromide it actually does not impact significantly on the overall yield of the reaction. The continual production of a clean gallium metal surface via slight heating is sufficient to ensure an efficient conversion of the aldehyde to the homoallylic alcohol. The low melting point of gallium therefore negates the need for sonication when using substituted allyl bromides, an option which is not practical for other metals we have thus far investigated, such as Sn.[2]

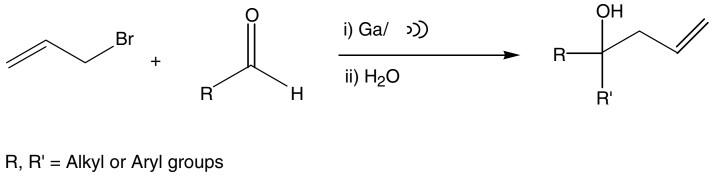
Table 1. Solvent-free allylation of various carbonyl compounds mediated by gallium metal

Carbonyl compounds	Isolated yield (%)[a]
PhCH=O	97
2-(MeO)–PhC(H)=O	86
PhC(H)=C(H)C(H)=O	74
Ph(Me)C=O	34
$(Ph)_2C$=O	<10[b]
2-(OH)PhC(H)=O	0[b]
4-(OH)PhC(H)=O	0[b]

[a] All products gave satisfactory IR, ^{1}H NMR and EIMS as compared to previously reported spectra.

[b] Estimated by ^{1}H NMR and GC–MS.

Slightly lower yields of ca. 74% were observed for the α,β-unsaturated aldehyde, cinnamaldehyde. However, in terms of selectivity only the 1,2-addition product was observed. Conversely, aldehydes containing –OH substitution were inert to this system, with both 2- and 4-hydroxy substituted benzaldehydes producing none of the desired homoallylic alcohol. This is consistent with the acidity of such substituted phenolic groups and studies showing that alkyl gallium compounds react selectively at the phenolic OH rather than adding to the carbonyl moiety.[11] Also, consistent with our previous analogous studies for Bi, Zn, In and Sn, reactions involving ketones undergo allylation to a much lesser extent (e.g., acetophenone ca. 30%). Ketones, such as benzophenone, which exhibit reduced electrophilicity, result in low yields, <10%, reflecting a lower reactivity of the carbonyl group. In comparison, similar reactions using an allylic gallium reagent in THF–hexane[12] and



Scheme 1. Solvent-free allylation of various carbonyl compounds mediated by gallium metal.

the gallium mediated allylation of carbonyl compounds in water[13] give similar or slightly improved yields. Another noteworthy observation is that no side products resulting from Wurtz or pinacol coupling are observed, only unreacted starting material being detected.

3. Solvent-free synthesis of imines

Traditionally imines have been synthesised via the addition of amines and carbonyl compounds under azeotropic conditions.[14] Recently, however, several benign synthetic protocols have been developed for the synthesis of imines including the use of a water suspension,[15] several solid state procedures including clay catalysed synthesis using microwave irradiation[16] and solid state synthesis involving ultra-high intensity grinding.[17] The imines in this study, listed in Table 2, were produced by grinding/mixing together various aldehydes with aniline in a mortar and pestle in the presence of a catalytic amount of toluene-4-sulfonic acid, Scheme 2.

Residual acid was removed by washing quickly with a small amount of water and the remaining solid product recrystallised from MeOH affording the desired imines in high yields, ca. 90–100%, Table 2. The reaction times of 10–30 min are on par with those previously reported, with only a slight reduction in yields observed for those imines derived from cinnamylaldehyde.[15–17] Although the water suspension method required no acidic catalyst to produce high yields, the procedure is obviously restricted to only hydrolytically robust C=N containing compounds such as the sulfonyl imines.[3] Moreover, the use of water as bulk solvent generates an aqueous waste stream, which is an important consideration when developing green chemistry reactions.[18]

4. Synthesis of homoallylic secondary amines

The reaction methodology, Scheme 2, which proved successful with various aldehydes, was repeated with the imines. The corresponding homoallylic amines were obtained in yields ranging from 32% to 94%, Table 3, for imines derived from aromatic, –OMe substituted aromatic and aliphatic aldehydes. These yields are comparable

Table 3. Synthesis of homoallylic secondary amines using gallium metal

Imine	Yield of homoallylic secondary amine (%)[a]
PhC(H)=NPh	94
4-(MeO)–PhC(H)=NPh	87
2-(MeO)–PhC(H)=NPh	72
2-(OH)–PhC(H)=NPh	<5[b]
PhC(H)=N–2,6-(Me)–Ph	44
$PhCH{=}NCH_2CH_2Ph$	32
$(Ph)_2C{=}NH$	<10[b]
PhC(H)=C(H)C(H)=NPh	0

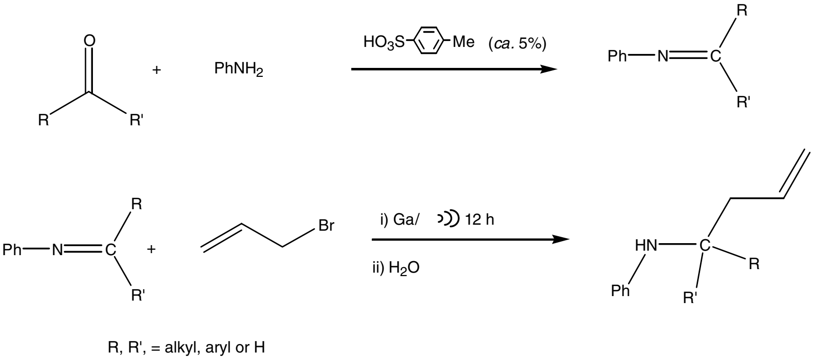
[a] All products gave satisfactory IR, ^1H NMR and EIMS as compared to previously reported data.

[b] Estimated by ^1H NMR and GC–MS.

Table 2. Synthesis of imines from amines using solventless protocols

Aniline	Aldehyde	Imine	Yield (%)[a]
$PhNH_2$	PhCH=O	PhC(H)=NPh	99
$PhNH_2$	2-(OH)–PhCH=O	2-(OH)–PhC(H)=NPh	97
$PhNH_2$	2-(MeO)–PhCH=O	2-(MeO)–PhC(H)=NPh	94
$PhNH_2$	4-(MeO)–PhCH=O	4-(MeO)–PhC(H)=NPh	96
$PhNH_2$	PhCH=CHCH=O	PhC(H)=C(H)C(H)=NPh	89
$PhCH_2CH_2NH_2$	PhCH=O	$PhCH{=}NCH_2CH_2Ph$	54
2,6-(Me)–$PhNH_2$	PhCH=O	PhCH=N–2,6-(Me)–Ph	46

[a] All products gave satisfactory IR, ^1H NMR and EIMS as compared to previously reported data.



Scheme 2. A two-step solvent-free route to homoallylic amines.

Table 4. Estimated yield of formation of bis-allylated (**2**) and mono-allylated (**1**) species under various conditions using indium metal as the mediator for the allylation of the imine *N*-benzylidene aniline

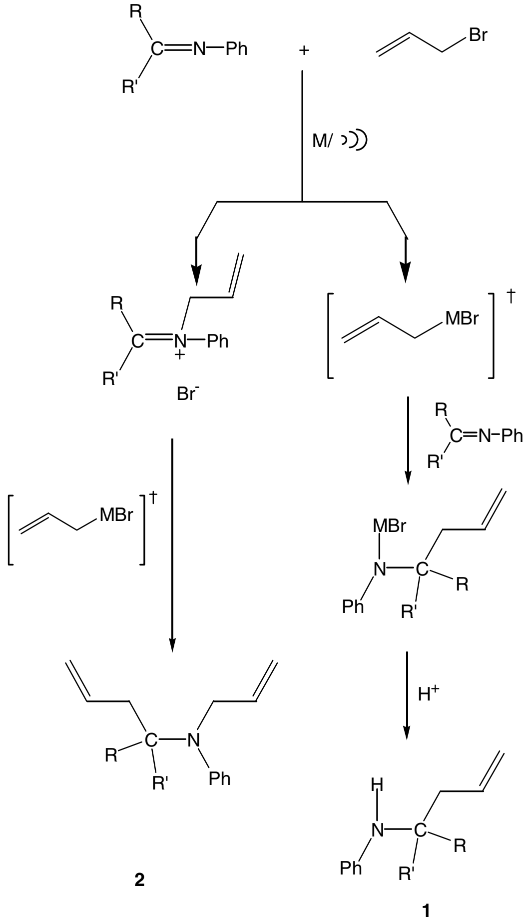
Entry	Method	Homoallylic alcohol[a]	Homoallylic secondary amine (**1**)[a]	Bis-allylated amine (**2**)[a]
1	1 equiv of allyl bromide	No reaction, recovery of starting material		
2	1.5 equiv of allyl bromide	31%	36%	32%
3	3 equiv of allyl bromide	15%	22%	63%
4	Generation of allyl indium species before quench	10%	89%	0%

[a] Estimated by ^{1}H NMR and GC–MS.

with the results of similar reactions with indium metal carried out in THF, DMF and alcoholic solvents.[19–21] Furthermore, in comparison to other organometallic allylation reactions there is no requirement for presynthesis of the allyl metallic species. The imines prepared from aromatic carbonyl compounds formed in the highest yields, while the α,β-unsaturated imine, unfortunately, produced only the homoallylic alcohol, presumably from allylation of the aldehyde derived from the gallium salt catalysed hydrolysis of the imine. For comparison, yields were substantially reduced for benzophenone imine (ca. <10%) again reflecting deactivation of the C=N bond. Similar to the –OH substituted aldehydes, imines derived from hydroxy substituted aldehydes did not undergo any 1,2-addition reactions.

5. Gallium versus indium

In an attempt to expand previous solvent-free reaction protocols for the allylation of carbonyl compounds mediated by indium metal, we investigated the solvent-free approach to the synthesis of allylamines. In these reactions, a mixture of the imine and indium powder, and 1.5 equiv of allyl bromide was sonicated for 12 h before quenching with water (ca. 0.5 mL). In comparison to the equivalent reactions mediated by gallium metal, indium metal produced surprising results. A mixture of products resulted, with the mono-allylated species, **1**, and the bis-allylated (allylphenyl-(1-phenyl-but-3-enyl)amine),[22] species, **2**, being detected and isolated using flash chromatography. Furthermore, according to GC–MS data the two products were each produced in approximately 40% yield, Scheme 3 and Table 4. The homoallylic alcohol is derived from the hydrolysis of any remaining imine and the subsequent reaction of the reformed aldehyde with the residual allyl indium halide species, which itself is relatively stable in an aqueous environment.



Scheme 3. Formation of bis-allylated amine in a solventless protocol with indium as the mediator.

In an attempt to prevent the bis-allylated species, **2**, being formed, and to elucidate the mechanism of its formation, the procedure was modified whereby only 1 equiv of the bromide was added initially (Table 4, entry 1). However, this resulted only in recovery of starting material, presumably due to the lack of allyl indium halide formation. Formation of bis-allylated **2** was entirely suppressed by addition of allyl bromide to indium metal prior to any addition of amine, thus allowing the allylic indium halide species to form before the addition of the imine (Table 4, entry 4).

The bis-allylated product, **2**, presumably arises from the formation of an iminium salt, which subsequently undergoes competitive nucleophilic attack from the allyl indium halide species, Scheme 3. This has been previously postulated as a possible route in similar allylation reactions,[23] and is further supported by the increase in yield, ca. 60%, of **2** when a large excess of allyl bromide is present (ca. 3 equiv), which encourages formation of the iminium salt. Given that iminium salts are observed when reacting alkyl halides and enamines under refluxing conditions,[24] we attempted to form deliberately the iminium salt via the addition of 1.5 equiv of MeI to *N*-benzylidene aniline at 50 °C in toluene for 24 h under an inert atmosphere. This resulted in the formation of the corresponding iminium salt in a 67% yield.[†] The possibility of the bis-allylated species arising from the reaction of unreacted allyl bromide and **1** after hydrolysis was discounted by the in vacuo removal of any excess allyl bromide prior to the aqueous quench, which still resulted in significant yields of the bis-allylated product.

Why is no bis-allylated product formed when gallium metal is used? This is still an intriguing question and one we are still attempting to understand. One possibility is that the allyl gallium halide species forms at a much faster rate than the iminium salt thus producing the homoallylic secondary amine. This would imply that although the two metals have similar first ionisation potentials, insertion of gallium into a carbon halogen bond in forming the reactive allyl metal halide species, and its subsequent reaction with the unsaturated bond, is significantly more facile than the corresponding process for indium. Another possible process could be that gallium in some way deactivates the N towards allylation through complexation or that the allyl bromide is bound up by the organogallium species in a way that does not occur with indium. The similarity in the chemical behaviours of the two metals makes these explanations, at first sight, counter-intuitive and so is the target of further investigation.

6. Experimental

6.1. Typical procedures

6.1.1. Synthesis of 1-phenyl-3-buten-1-ol. In a Schlenk flask under a nitrogen atmosphere, a suspension of 5 mmol (0.35 g) of gallium metal and 5 mmol (0.53 g) of benzaldehyde, was allowed to stir rapidly. To this suspension 7.5 mmol (0.91 g) of allyl bromide was added and allowed to react via sonication for 12 h, resulting in the production of a brown oil and the complete consumption of the gallium metal. This was then quenched with 0.5 mL of H_2O. The reaction mixture was then extracted with 3 × 10 mL of diethyl ether, with the ethereal layers being combined and dried over $MgSO_4$. The solution was then filtered and reduced under reduced pressure, to give a colourless oil. The homoallylic alcohol was isolated by flash chromatography on silica gel using a 10:1 ratio of hexane to ethyl acetate in 97% yield. Spectral data of this compound was in accordance with that previously reported.[25]

6.1.2. Synthesis of phenyl-(1-phenyl-but-3-enyl)-amine. To a mixture of 0.11 g of gallium metal (1.6 mmol) and 0.28 g of benzylidene aniline (1.6 mmol), 1.5 equiv of allyl bromide (0.29 g/2.4 mmol) was added dropwise under an atmosphere of argon. This was allowed to sonicate for 12 h, which resulted in the complete consumption of gallium metal and the formation of a dark yellow oil. The reaction was then quenched with H_2O (ca. 0.5 mL) and allowed to sonicate for a further 15 min. The reaction mixture was extracted with diethyl ether (3 × 15 mL), with the combined organic layers being dried over $MgSO_4$. This was then purified by Kugelrohr distillation under high vacuum to afford the desired homoallylic secondary amine as a clear yellow oil. The spectral data of this compound was consistent with data that had been previously reported.[26]

6.1.3. Synthesis of allylphenyl-(1-phenyl-but-3-enyl)-amine. To a mixture of 0.32 g of indium metal (2.7 mmol) and 0.50 g of benzylidene aniline (2.7 mmol), 1.5 equiv of allyl bromide (4.5 mmol) was added dropwise under an atmosphere of argon. This was allowed to sonicate for 12 h, which resulted in the complete consumption of indium metal and the formation of a dark yellow oil. The reaction was then quenched with H_2O (ca. 0.5 mL) and allowed to sonicate for a further 15 min. The reaction mixture was extracted with diethyl ether (3 × 15 mL), with the combined organic layers being dried over $MgSO_4$. This was then purified by flash chromatography on silica, using 10:1 hexane–ethyl acetate on silica gel, to give the bis-allylated product as a clear yellow oil in 28% yield. Spectral data of this compound was in agreement with data that had been previously reported for this compound.[27]

Reactions employing sonication were performed in the Transtek Systems, Soniclean 80T model. This sonicator runs at 240 V with and operating frequency of 50–60 Hz. GC–MS data were obtained on the Aligent 6890 Series GC Systems and the Aligent 5973 Network Mass Selective Detector. Aliquots of the samples (1 μL) were injected, with inlets having a split ratio of 25:1. Helium gas was employed at a pressure set at 7.16 psi and flow rate 26.6 mL/min. The installed column was the HP-5MS 5% phenyl methyl siloxane with a capillary size of 30.0 m × 250 μm × 0.25 μm. The oven setpoint was 60 °C (held for 3 min) increasing at a rate of 10 °C/min to the endpoint of 280 °C. ^1H NMR spectra of compounds were recorded in $CDCl_3$ on the Varian Mercury 300 at 400 MHz. Infra-red spectra were obtained on a Perkin–Elmer 1600 FTIR.

Acknowledgements

We thank the Centre for Green Chemistry at Monash University and the Australian Research Council for their financial support.

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[†] Recrystallised from toluene in 67% yield. ^1H NMR (benzene-d_6, 30 °C, 300 MHz) δ 8.38 (1H, s, CH), 7.18 (10H, m, aromatic H), 0.45 (3H, s, $-CH_3$).

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