Microwave-induced organometallic reactions in aqueous media. Use of Ga and Bi for the allylation of aromatic *N*-oxides and hydrazones

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Homoallylic hydroxylamines and homoallylic hydrazides were synthesised in excellent yields by the reaction of allylgallium or allylbismuth reagent, generated *in situ* in the presence of 0.1 equivalent of NH_4Cl–Bu_4NBr, with aldonitrones and hydrazones in aqueous media. The reaction rate can be increased dramatically under microwave activation.

Scheme 1

There has been growing interest in the use of metallic elements[1] in aqueous media, as they offer significant advantages over conventional reactions using dry organic solvents. The development of such reactions is of interest because they also offer the possibility of obtaining environmentally benign reaction conditions by reducing the burden of organic solvent disposal.[2] The study and application of Barbier–Grignard type reactions[3] in water is still in its infancy. Since their history is only a decade old, the full synthetic potential of such reactions is still waiting to be explored and they need to be expanded.[4] The application of the Grignard reaction in carbon–carbon bond-forming reactions for large-scale industrial application is limited[5] by the expense of the metal, the anhydrous ether solvents required and complications of waste solvent disposal. Also, the addition of organometallic reagents to the C=N double bonds of imines or hydrazones has been severely affected both by the poor electrophilicity of the azomethine carbon and by the tendency of enolisable imines and imine derivatives to undergo deprotonation rather than addition.[6] Nitrones possess the most highly polarised C=N double bond, which is responsible for their good electrophilic reactivity, and a reactive oxygen atom, making them capable of reacting with organometallic compounds to generate a host of products bearing the homoallyl group. In continuation of our studies on metal-mediated organic reactions,[7] we report herein the first example of gallium and bismuth-mediated allylation of various aldonitrones and hydrazones derived from aromatic aldehydes under microwave irradiation. We paid particular attention to gallium, a soft low valent and comparatively less studied element of group IIIA; there have been only a few examples of synthetic reactions in the literature[8] using gallium, which belongs to the same group as the extensively studied boron, aluminium and indium[9] elements.

Reaction of aldonitrone **1** with allylic bromide in the presence of gallium or bismuth and ammonium chloride in DMF–H_2O (3 : 1) as the solvent (Scheme 1) produced the corresponding homoallylic hydroxylamines **2** in 60–75% yields. Analysis of the crude mixture did not indicate the formation of any other products. Similarly, allylgallium or allylbismuth reagent stoichiometric amount, (*in situ* generated) undergo addition to the carbon–nitrogen double bond of aryl or tosyl
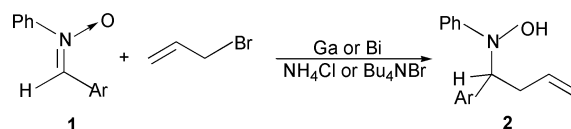
hydrazones **3** in a NH_4Cl (or Bu_4NBr)–DMF–water system (Scheme 2) to provide the corresponding homoallyl hydrazides **4** and **5** in 60–65% yields after 6–12 h. The reaction proceeds conveniently and no trace of *N*-allylated product could be detected. Furthermore, it is to be noted that in aqueous media many imines are hydrolysed to the corresponding carbonyl compounds before allylation occurs, thus giving the homoallylic alcohols.[2] Also it is remarkable to note that indium[10] enhances the homocoupling of imines in aqueous media to give the corresponding 1,2-diamines. But with gallium or bismuth in our reaction conditions, we have not observed the formation of any hydrolysed products or 1,2-diamines. Moreover, the reaction time is reduced dramatically from 6–12 h to 4–5 min when the same experiment was performed in a domestic microwave oven,[11] operating at 2450 MHz frequency. Excellent yields are obtained ($\geqslant 80\%$, see Table 1).

The use of NH_4Cl was found to be important, as the allylation did not proceed at all with gallium or bismuth alone, without NH_4Cl. It is obvious that activation of the metal is needed for this reaction to proceed. Therefore, we tried a number of alkaline metal salts like NaBr, KBr, $MgBr_2$ and KCl in aqueous media as additives in place of NH_4Cl and found these to be ineffective or to give poor yields. However, Bu_4NBr was found to quite effective in activating the gallium or bismuth to give a good yield of the corresponding homoallylic hydroxylamines and hydrazides. Roughly 0.1 equiv. of NH_4Cl was found to be sufficient for these reactions and use of a large excess did not lead to either higher yields or faster reaction rates. We thus used NH_4Cl or Bu_4NBr in the standard reaction conditions to activate commercial gallium or bismuth
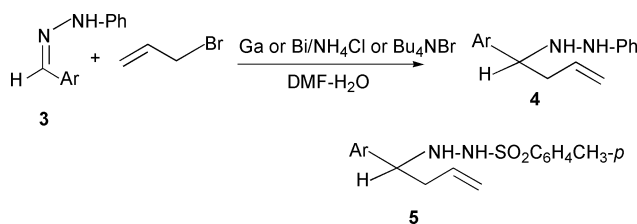
Scheme 2

Table 1 Ga or Bi/NH_4Cl mediated allylation of *N*-oxides and hydrazones[a]

Product	Ar	Room temperature				Microwave activation			
		Reaction time/h		Yield (%)		Reaction time/min		Yield (%)	
		Ga	Bi	Ga	Bi	Ga	Bi	Ga	Bi
2a	C_6H_5	6	9	65	75	4	4	90	95
2b	4-ClC_6H_4	7	9	68	70	5	4	92	85
2c	4-$CH_3C_6H_4$	6	10	63	70	5	5	86	90
2d	2-Furyl	7	8	62	70	5	4	80	85
2e	2-Thienyl	7	12	60	65	5	5	80	83
2f	4-$CH_3OC_6H_4$	7	10	60	75	4	5	85	80
2g	3-$NO_2C_6H_4$	8	8	60	70	4	5	83	80
4a	C_6H_5	6	11	62	65	5	5	80	85
4b	4-ClC_6H_4	7	12	60	60	5	5	92	85
4c	4-$CH_3C_6H_4$	7	12	60	60	5	5	93	80
4d	4-$CH_3OC_6H_4$	7	11	62	65	4	5	80	82
4e	C_6H_5	6	10	60	65	4	5	83	85
4f	4-ClC_6H_4	6	11	63	65	4	5	80	83
5	C_6H_5	6	12	65	62	5	5	84	85

[a] All the products were characterised by ^{1}H NMR and mass spectrometry and by comparison with authentic samples.

metal and examined its reaction with a number of substrates. It is interesting to note that the nature of the solvent controlled the formation of homoallylated products. The reaction failed to produce any desired compound when THF–H_2O (3 : 1) or THF alone was used as the solvent. Also, no isolable product was formed when the reaction was run in water or DMF alone. An organic solvent is required for the reaction to proceed. After screening the reaction conditions, the optimum medium for this allylation reaction seems to be a 3 : 1 mixture of DMF–H_2O.

The results in Table 1 reveal the generality of this methodology in terms of structural variations of the nitrone moiety; in each case homoallylic hydroxylamines were isolated in excellent yields. Furthermore, electron-donating or -withdrawing groups on the aromatic ring do not seem to affect the reaction significantly, either in the yield of the product or the rate of the reaction. Moreover, the nitro function was not reduced under the reaction conditions. Thus, 3-nitrobenzaldehyde nitrone **2g** was successfully allylated. Usually, the nitro group is sensitive to reduction by metals and cannot be allylated under Barbier conditions.[10] In this sense, the use of an additive as an activating agent is superior to the use of Al, Fe or $NaBH_4$ reported previously.[12] Although the detailed mechanism of the reaction is not clear, it is likely that NH_4Cl or Bu_4NBr affects the generation of an active organogallium or organobismuth reagent. All the compounds obtained were characterised by infrared and ^{1}H NMR spectroscopy and finally by comparison with authentic samples.

In conclusion, this simple and easily reproducible technique using gallium or bismuth[13] in aqueous conditions and under microwave irradiation affords various homoallyl hydrazides and hydroxylamines of potentially high synthetic utility in excellent yields and without the formation of any undesirable side products.

Experimental

Melting points were determined using a Buchi melting point apparatus and are uncorrected. IR spectra were recorded for KBr discs on a Perkin–Elmer 240C analyser. ^{1}H NMR spectra were recorded on 60 MHz spectrometers and chemical shift values are recorded in δ relative to Me_4Si as internal standard. Solvents used were dried according to literature procedures. All reagents were of commercial quality from freshly opened containers and were purchased from Aldrich Chemical

Company and Central Drug House (Pvt.) Ltd. (New Delhi), and used without further purification. All the carbonyl compounds and phenylhydroxylamines used were freshly distilled and recrystallised before use and their properties checked by spectroscopic data.

General procedure for the allylation of aldonitrones 1, aryl and tosyl hydrazones 3 at room temperature

A suspension of bismuth powder (2.08 g, 10 mmol), allyl bromide (1.8 g, 15 mmol) and ammonium chloride (55 mg, 1 mmol) was taken up in 20 ml of DMF–H_2O (3 : 1) in a 150 ml round-bottomed flask and was stirred at room temperature until the metal was completely dissolved. To the allylbismuth reagent generated, a solution of aldonitrone **1a** (2.0 g, 10 mmol) in 5 ml DMF was added. The resulting mixture was stirred at room temperature for 9 h. The reaction was then quenched with diluted HCl, followed by extraction with ether (2 × 20 ml). The combined ether extract was washed with brine, dried over anhydrous sodium sulfate and the residue obtained thereafter on evaporation of the solvent was chromatographed using ethyl acetate–hexane (1 : 5) to afford the pure homoallyl product **2a** in 75% yield. Similarly, other aldonitrones **1b–g** and hydrazones **3a–f** were reacted in the presence of gallium or bismuth metal and ammonium chloride and the reaction characteristics are recorded in Table 1. All the compounds obtained were characterised by infrared and ^{1}H NMR spectroscopy and finally by comparison with authentic samples. The reaction was found to be equally effective when 0.1 equiv. of Bu_4NBr was used in place of NH_4Cl and the corresponding homoallyl hydroxylamines were isolated in 60–70% yields.

2a: ^{1}H NMR ($CDCl_3$): δ 6.62–7.25 (m, 11H, ArH and OH), 5.72–5.90 (m, 1H), 5.12–5.35 (m, 2H), 4.32 (t, $J = 7.2$, 1H), 2.62–2.78 (m, 2H). MS: m/z 238.

General procedure for the allylation of aldonitrones, aryl and tosyl hydrazones under microwave irradiations using Ga or Bi

In a typical procedure, a mixture of bismuth powder (2.08 g, 10 mmol), allyl bromide (2.4 g, 20 mmol), ammonium chloride (55 mg, 1 mmol) and hydrazone **3a** (2.0 g, 10 mmol) in 20 ml DMF–H_2O (3 : 1) was placed in an Erlenmeyer flask and heated in a commercial microwave oven operating at 2450 MHz frequency for 5 min (monitored by TLC). The reaction was then quenched with diluted HCl, followed by extraction

with ether (2 × 20 ml). The combined ether extracts were washed with brine, dried over anhydrous sodium sulfate and the residue obtained on evaporation of the solvent was chromatographed using ethyl acetate–hexane (1 : 5) to afford the corresponding homoallyl hydrazide product **4a** in 85% yield. Similarly, other aryl and tosyl hydrazones and aldonitrones were reacted with gallium and bismuth in the presence of ammonium chloride under microwave irradiation and the reaction characteristics are recorded in Table 1.

4a: ^{1}H NMR (CDCl$_3$): δ 8.72 (br, NH), 7.05–7.35 (m, 10H, ArH), 5.70–5.92 (m, 1H), 5.05–5.22 (m, 2H), 4.17 (t, $J = 7.2$, 1H), 2.45–2.60 (m, 2H). MS: m/z 238.

References

1   D. G. Tuck, in *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, Pergamon Press, New York, 1982, vol. 1, pp. 683–723.

2   C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; H.-U. Reissig, *Organic Synthesis Highlights*, VCH, Weinheim, 1991, p. 71; C.-J. Li, *Chem. Rev.*, 1993, **93**, 2023; A. Lubineau, J. Auge and Y. Queneau, *Synthesis.*, 1994, 741; C.-J. Li, *Tetrahedron*, 1996, **52**, 5643.

3   For the Barbier type allylation using Bi see: A. R. Katritzky, N. Shobana and P. A. Harris, *Organometallics*, 1992, **11**, 1381; using Sn see: D. Marton, D. Stivanello and G. Tagliavini, *J. Org. Chem.*, 1996, **61**, 2731; using Pb see: H. Tanaka, S. Vamashita, T. Hamatani, Y. Ikemoto and S. Torii, *Chem. Lett.*, 1986, 1611; using Mg see: F. Barbot and P. Miginiac, *Tetrahedron Lett.*, 1975, **44**, 3829; using Cd see: B. Sain, D. Prajapati and J. S. Sandhu, *Tetrahedron Lett.*, 1992, **33**, 4795; using Ce see: T. Imamoto, T. Kashumo, Y. Tuosorayama, T. Mita, Y. Hatanaka and M. Yokayoma, *J. Org. Chem.*, 1984, **49**, 3904; using Sb see: W. Wang, L. Shi and Y. Huang, *Tetrahedron*, 1990, **46**, 3315; using In see: C. J. Li and T. H. Chan, *Tetrahedron Lett.*, 1991, **32**, 7017; L. A. Paquette, G. D. Bennett, M. B. Isaac and A. Chhatriwalla, *J. Org. Chem.*, 1998, **63**, 1836; using Ta see: P. J. Bhuyan, D. Prajapati and J. S. Sandhu, *Tetrahedron Lett.*, 1993, **34**, 7975; using Ge see: T. Akiyama, J. Iwai, Y. Onuma and H. Kagoshima, *Chem. Commun.*, 1999, 2191.

4   Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207.

5   T. D. Waugh, *Kirk–Othmer Encyclopedia of Science and Technology*, J. Wiley, New York, 3rd edn., 1980, p. 230.

6   R. Bloch, *Chem. Rev.*, 1998, **98**, 1407.

7   B. Baruah, A. Boruah, D. Prajapati and J. S. Sandhu, *Tetrahedron Lett.*, 1997, **38**, 1449; B. Baruah, A. Boruah, D. Prajapati and J. S. Sandhu, *Tetrahedron Lett.*, 1996, **37**, 9087; D. Prajapati, D. D. Laskar and J. S. Sandhu, *Tetrahedron Lett.*, 2000, **41**, 8639.

8   K. Saigo, Y. Hashimoto, N. Kihara, H. Umehara and M. Hasegawa, *Chem. Lett.*, 1990, 831; K. Saigo, Y. Hashimoto, N. Kihara, K. Hara and M. Hasegawa, *Chem. Lett.*, 1990, 1097; M. Falorni, L. Lardicci and G. Giacomelli, *Tetrahedron Lett.*, 1985, **26**, 4949; S. Araki, H. Ito and Y. Batsugan, *Appl. Organomet. Chem.*, 1988, **26**, 475; S. Kobayashi, K. Koide and M. Ohno, *Tetrahedron Lett.*, 1990, **31**, 2435; S. Murahashi, H. Mitsui, T. Shiota, T. Tsuda and S. Watanabe, *J. Org. Chem.*, 1990, **55**, 1736; M. Shibasaki, H. Sasai and T. Arai, *Angew. Chem., Int. Ed.*, 1997, **36**, 1236.

9   For very recent reviews on indium metal see: K. K. Chouhan and C. G. Frost, *J. Chem. Soc., Perkin Trans. 1.*, 2000, 3015; C.-J. Li and T.-K. Chan, *Tetrahedron*, 1999, **55**, 11 149.

10 N. Lalyanam and G. V. Rao, *Tetrahedron Lett.*, 1993, **34**, 1647.

11 For the use of microwave energy to activate organic reactions and its superheating or acceleration effects see: M. Majdoub, A. Loupy, A. Peter and M. S. Roudesli, *Tetrahedron*, 1996, **52**, 617 and references cited therein; S. Caddick, *Tetrahedron*, 1995, **51**, 10 403; D. M. Mingos and D. R. Baghurst, *Chem. Soc. Rev.*, 1991, **20**, 1; R. J. Giguere, *Organic Synthesis: Theory and Application*, Jai Press, Greenwich, UK, 1989, vol. 1, p. 103; A. K. Bose, M. S. Manhas, M. Ghosh, M. Shalt, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, A. G. Choudhury and K. I. Borakat, *J. Org. Chem.*, 1991, **56**, 6968.

12 R. A. Valkmann, in *Comprehensive Organic Synthesis, Addition to C–X π Bonds, Part I*, ed. S. L. Schreiber, Pergamon, Oxford, 1991, vol. 1, pp. 355–396.

13 For a review on recent developments on bismuth metal see: S. Vidal, *Synlett*, 2001, 1194.