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Microwave Assisted Regioselective Bromomethoxylation of Alkenes Using Polymer Supported Bromine Resins

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Abstract: A facile regio- and chemoselective bromomethoxylation of alkenes under microwave irradiation conditions employing a new polymer supported brominechloride resin is reported. The resin is prepared from the commercially available chloride resin by a simple one step procedure.

Keywords: Bromomethoxylation; polymer supported bromine resins; microwave irradiation

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Introduction

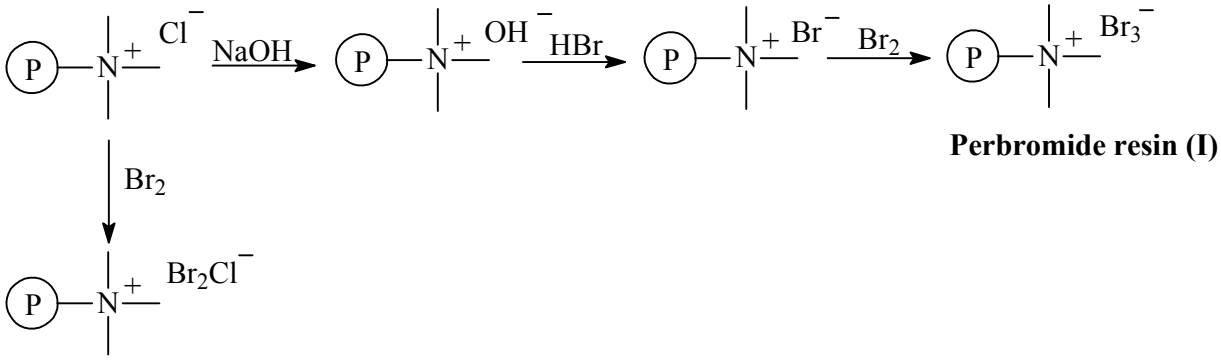
Application of polymer-supported reagents in organic synthesis has grown over the years due to its convenient handling and easy work up procedures [1]. The importance of these reagents is much felt in the new approach of combinatorial synthesis, where high throughput solution phase synthesis is designed with polymer supported reagents [2]. The present study demonstrates the stability of the new polymer supported bromine chloride resin and the previously reported perbromide resin [3] to microwave irradiation conditions. A facile regio and chemo selective bromomethoxylation of a variety of alkenes employing the above reagents is reported, including examples from natural sources.

Results and Discussion

In our continuing study on the functionalisation of isoprenyl coumarins [4] directed towards identifying bioactive leads, the bromomethoxylation of osthol (**9**) was attempted. The available cohalogenating reagents, namely bromine in methanol [5], NBS/methanol [6] and N-bromoacetamide/ methanol [7] on reaction with **9,** either resulted in multiple products or posed problems during isolation of the desired product. Hence, an attempt was made to apply the polymer supported perbromide resin (**I**), for the desired reaction. Resin **I** has been reported to effect the bromination of phenols [8] and ketones [9]. When **9** was treated with resin **I** in methanol, at either room temperature or under reflux conditions, bromomethoxylated product along with the corresponding bromohydroxy compound were obtained. The formation of bromohydroxy compound was rationalized as due to a demethylation of the bromomethoxy compound by the liberated HBr during the course of the reaction. However, when the reaction mixture was subjected to microwave irradiation (MWI), the reaction proceeded quantitatively within 30 seconds yielding the desired bromomethoxy compound. Hence a detailed study employing polymer supported reagents under MWI was taken up with other alkenes.

The preparation of the perbromide resin has been reported [8] from the commercially available IRA 400® chloride exchange resin by successive treatments with aq.NaOH, aq.HBr and Br_2/CCl_4 as depicted in **Scheme 1**. An alternative and hitherto unreported polymer supported bromine resin, the brominechloride resin (**II**) was successfully prepared by a simple one step procedure from the commercially available chloride resin. (**Scheme 1**)

Scheme1



Perbromide resin (I)

Brominechloride resin (II)

Both the resins **I** and **II** were found to possess the same amount of bromine and there was no appreciable change in the bromine content of these resins even after irradiating under MWI for 5 minutes as evident from the results reported in **Table 1**.

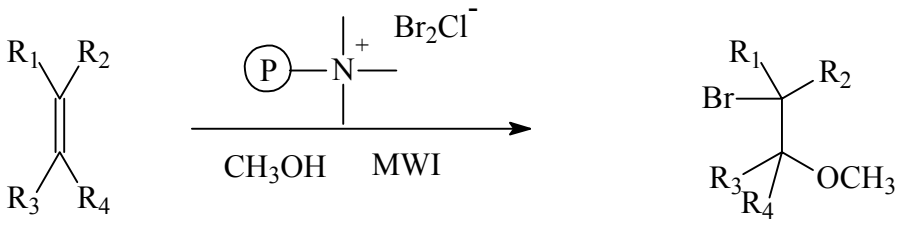
Table1: Bromine content of the resins after MWI*.

S.No	MWI (min)	Perbromide resin (mmol/g)	Brominechloride resin (mmol/g)
1	0	1.656	1.605
2	0.5	1.652	1.592
3	2	1.628	1.571
4	5	1.601	1.518

* 2g of the resin in 10 ml of methanol was irradiated in a modified microwave oven [10] and then analyzed for bromine content. MWI- microwave irradiation.

Various substituted alkenes: monosubstituted-1-decene (**1**); disubstituted- isoprenol (**2**); methyl angolensate, (**3**); carvone, (**4**); azadirachtin-A, (**5**); trisubstituted- prenol, (**6**); 2-(3-methylbutenyl)-1-methoxybenzene, (**7**); 4-(3-methylbutenyl)-1-methoxy-benzene, (**8**); osthol, (**9**); tetra substituted - 2,3-dimethylbutene, (**10**), yielded the respective bromomethoxyalkanes in moderate to good yields on treatment with the resins **I** or **II** in methanol under microwave irradiation in a shorter reaction time (**Scheme 2**).

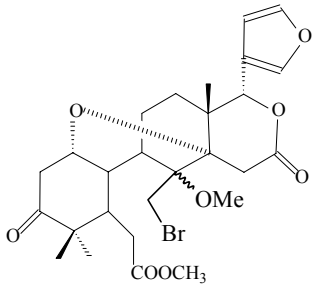
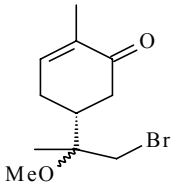
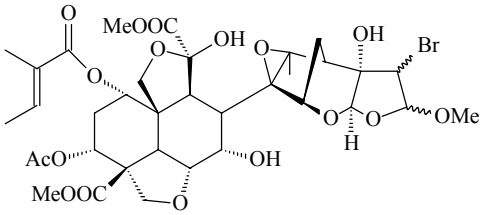
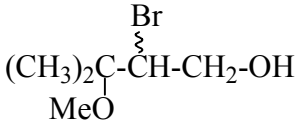
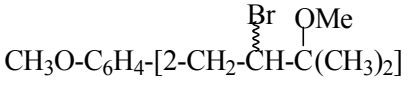
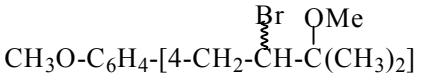
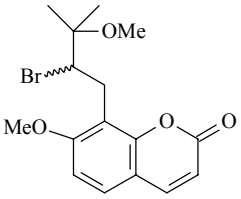
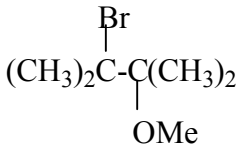
Scheme 2



The results are presented in the following table. (**Table 2**)

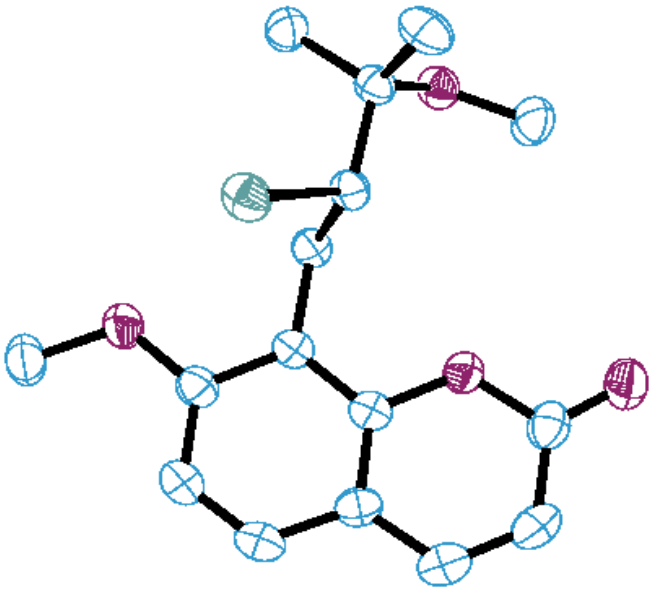
Table 2: Bromomethoxylation of alkenes with perbromide resin (**I**) and brominechloride resin (**II**) under microwave irrdiation**.**

Alkene	Product	Perbromide resin (I)		Brominechloride resin (II)	
		Time(min)	Yield(%)	Time(min)	Yield(%)
1	CH_3-$(CH_2)_7$-CH(OMe)-CH_2-Br **1a**[11]	5	68	5	57
2	Br-CH_2-C(OMe)(CH_3)-CH_2-CH_2-OH **2a**	5	61	5	65

3	 **3a**	2	85	3	80
4	 **4a**[12]	5	71	5	75
5	 **5a**	1	85	2	90
6	 **6a**	5	63	5	65
7	 **7a**	0.5	92	0.5	>95
8	 **8a**	0.5	90	0.5	92
9	 **9a**	0.5	>95	0.5	>95
10	 **10a**[13]	5	40	5	52

All the products were fully characterized by their spectral data (^{1}H-,^{13}C-NMR and MS). For one of the products (**9a**), the structure was also solved by X-ray crystallography [14] (**Figure 1**).

Figure 1: ORTEP diagram of compound **9a** drawn at 30% probability.



The reaction was found to be regioselective, following Markovnikov's addition rules, and also chemoselective as exemplified in the reaction of alkenes **4** and **5** where only the isolated double bonds were bromomethoxylated and the conjugated double bonds were inert to the reaction conditions. All the natural products considered for the present study (**3, 4, 5, 9** and **10**) gave high yields of the corresponding bromomethoxy compound in a very short reaction time. Successive washings of the resin with methanol, acetonitrile and chloroform and then passing bromine in CCl_4 through the resin, regenerated the polymer supported bromine reagent.

Conclusions

The present study illustrates a highly regio and chemoselective functionalisation of alkenes at short reaction times by the application of MWI to polymer supported reagents.

Acknowledgements

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Experimental

General

A modified domestic microwave oven (IFB-Megatron, wattage-1100W, power max-750W, voltage-230Hz, frequency-2450MHz) equipped with a refluxing unit was used. NMR spectra were recorded on a Bruker 200 MHz instrument using TMS as the internal reference for both ^{1}H- and

^{13}C-NMR experiments. $CDCl_3$ was used as the solvent. Chemical shifts are given in terms of parts per million (δ scale). MS analyses were recorded on a Shimadzu QP 5000 instrument. A DB-1 capillary column (30 meters length, 0.25 i.d) was used for all the GC analysis. Mass spectra were recorded in the EI mode. Precoated thin layer chromatography plates (E-merck, Germany, Keiselgel 60 F_{254}, 0.2 mm thickness, coated on aluminum sheets) were used. Column chromatography was performed using silica gel (60-120 mesh). IRA 400 Cl^- ® (product equivalent to Amberlyst-26, Fluka) was obtained from SD Fine Chemicals Ltd., India.

Preparation of Brominechloride resin (**II**). Oven dried IRA-400® (25g; Cl^- form) was packed in a column plucked with cotton on both the ends. A solution of bromine (8g; 0.05mol) in CCl_4 (100 ml) was passed through the column till the color of the resin turned yellow-orange. Then the column was washed with CCl_4 till all the free bromine was washed off and the washings were colorless. The resin beads were dried in a vacuum oven at 60°C for 3 hours.

Bromomethoxylation of alkenes: general procedure. To a solution of alkene (1 mmol) in methanol (10mL), was added the polymer supported reagents **I** or **II** (1g, containing 0.256g of bromine, 1.6 mmol) and irradiated in a modified domestic microwave oven fitted with a refluxing unit. After the reaction was complete (TLC), the reaction mixture was filtered; the resin was washed with methanol (3 x 10 ml). The filtrate was evaporated and the residue was purified by vacuum liquid chromatography (Si gel 230-400 mesh, eluent-Ethyl acetate: hexane) for the compounds **3a**, **5a**, **7a**, **8a** and **9a** and by column chromatography (Si gel 60-120 mesh, eluent: ethyl acetate-hexane) for **1a**, **2a**, **4a**, **6a** and **10a** to yield pure products respectively.

Spectral data:

1-Bromo-4-hydroxy-2-methoxy-2-methylbutane (**2a**): MF- $C_6H_{13}BrO_2$: LRMS(EI;m/z)-196, 198 (5.68% : 5.67%). ^{1}H-NMR: 1.20 (3H; s), 1.93 (1H; s), 2.14 (2H; t, J= 5.7Hz), 3.36 (3H; s), 3.42 (2H; s), 4.21(2H; t, J= 5.7Hz). ^{13}C-NMR: 24.4, 29.6, 43.7, 57.4, 59.6, 61.2.

3-0-bromo-8-methoxymethylangolensate (**3a**): MF- $C_{27}H_{35}BrO_8$: LRMS(EI;m/z)-566, 568 (2.68% : 2.67%); ^{1}H-NMR: 0.86 (3H, s), 0.90 (3H, s), 1.08 (3H, s), 1.14 (1H, m), 1.17 (3H, s), 1.21 (1H, m), 1.28 (1H, m), 2.16(1H, m), 2.18 (1H, m), 2.25 (1H, m), 2.56 (1H, m), 2.85 (1H, m), 2.89 (1H, m), 2.94 (1H, m), 3.18 (3H, s), 3.31 (2H, s), 3.46 (1H, dd, J= 6.1Hz and 3.7Hz), 3.70 (3H, s), 5.63 (1H, s), 6.29 (1H, d, J= 6.1Hz), 7.26 (1H, s), 7.39 (1H, dd, J= 6.2 and 3.4Hz); ^{13}C-NMR: 23.3, 28.8, 32.8, 33.6, 35.2, 39.5, 42.8, 43.9, 47.8, 49.3, 51.9, 57.2, 73.1, 78.1, 79.5, 139.5, 142.5, 146.6, 169.5, 173.5, 212.7, 26.5, 21.4, 21.2, 13.5.

22-Bromo-23-methoxyazadirachtin-A (**5a**): MF-$C_{36}H_{47}BrO_{17}$: LRMS(EI; m/z)-830, 832 (1.25% : 1.27%). ^{1}H-NMR: 1.33 (1H, d, J= 5.8Hz), 1.73 (1H, d, 5.7Hz), 1.74 (3H, s), 1.78 (3H, dq), 1.85 (3H, dq), 1.95 (3H, s), 2.01 (3H, s), 2.15 (1H, m), 2.31 (1H, m), 2.38 (1H, d, J= 7.1Hz), 2.56 (1H, m), 2.58 (1H, m), 2.84 (1H, d, J=7.1Hz), 2.90 (1H, bs), 3.33 (1H, s), 3.38 (3H, s), 3.37 (1H, d, J=6.5Hz), 3.64 (1H, d, J=6.1Hz), 3.68 (3H, s), 3.75 (1H, d, J=6.5Hz), 3.79 (3H, s), 4.09 (1H, d, J=6.1Hz), 4.17 (1H,d, J=3.8Hz), 4.58 (1H, dd, J=4.5 and 7.8Hz), 4.67 (3H, s), 4.76 (1H, d, J=3.7Hz), 4.77 (1H, d, J=4.5Hz), 5.50 (1H, dd, 3.8 and 7.7Hz), 6.94 (1H, dd, J=6.1 and 7.4 Hz): ^{13}C-NMR: 11.9, 14.3, 18.1, 20.8, 21.8, 29.6, 37.0, 45.6, 47.6, 50.2, 52.3, 52.7, 53.3, 57.4, 57.6, 66.9, 67.7, 68.6, 69.1, 70.3, 73.0, 74.2, 76.3, 78.2, 102.7, 104.1, 110.3, 128.5, 137.7, 166.2, 169.6, 171.7, 173.3.

2-Bromo-3-methoxy-3methylbutanol (**6a**): MF- $C_6H_{13}BrO_2$: LRMS(EI; m/z)-196, 198 (6.32% : 6.32%). ^{1}H-NMR:1.7 (3H; s), 1.82 (3H; s), 2.24 (1H; bs), 3.40 (3H, s), 3.91 (1H; t, J= 7.3Hz), 4.49 (2H; d, J=7.2Hz); ^{13}C-NMR: 29.4, 35.2, 65.8, 68.8, 83.7.

2-(2-Bromo-3-methoxy-3-methylbutyl)-1-methoxybenzene (**7a**): MF- $C_{13}H_{19}BrO_2$: LRMS(EI; m/z)-286, 288 (4.65% : 4.64%); ^{1}H-NMR: 1.26 (6H; s), 2.73 (2H; m), 3.25 (3H; s), 3.78 (3H; s), 4.1 (1H; dd, J= 6.1 and 3.9 Hz), 6.8 (2H; m), 7.2 (2H; m); ^{13}C-NMR: 21.2, 22.4, 27.0, 49.6, 55.7, 59.7, 77.4, 115.6, 119.6, 127.1, 142.8.

4-(2-Bromo-3-methoxy-3-methylbutyl)-1-methoxybenzene (**8a**): MF- $C_{13}H_{19}BrO_2$: LRMS (EI; m/z)-286, 288 (7.51% : 7.51%); ^{1}H-NMR: 1.21 (6H; s), 2.86 (2H; m), 3.30 (3H; s), 3.83 (3H; s), 4.26(1H; dd, J=6.3 and 3.9Hz), 6.8 (2H; d, J=7.8Hz), 7.3 (2H; d, J=7.8Hz); ^{13}C-NMR: 21.4, 22.6, 27.3, 48.7, 55.9, 59.9, 77.2, 115.8, 120.1, 127.2, 143.4.

7-Methoxy-8-(2-bromo-3-methoxy-3-methylbutyl)coumarin (**9a**): MF- $C_{16}H_{19}BrO_4$: LRMS (EI; m/z)-354, 356 (3.35% : 3.36%); ^{1}H-NMR: 1.32 (3H; s), 1.44 (3H; s), 3.40 (3H; s), 3.52 (2H; m), 3.96 (3H; s), 4.61 (1H; dd, J= 4.5 and 5.2Hz), 6.20 (1H; d, J=6.9Hz), 6.85 (1H; d, J=7.4Hz), 7.42 (1H; d, J=6.9Hz), 7.6 (1H; d, J=7.4Hz); ^{13}C-NMR: 22.3, 23.6, 26.8, 49.6, 56.0, 60.5, 77.2, 107.4, 113.0, 115.6, 119.5, 127.1, 143.7, 160.6; *Crystal data:* [14] Triclinic, P-1, a = 10.280 (2) Å, b = 10.497 (4) Å, c = 16.175 (4) Å, α = 75.91 (2)˚, β = 80.81 (2)˚, γ = 68.00 (3)˚, V = 1565.1 (8) Å^3, λ = 1.54184 Å, R = 0.0638.

References and Notes

1. Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis,* **2000**, 1035-1074.
2. Bhalay, G.; Dunstan, A.; Glen, A. *Synlett*., **2000**, *12*, 1846-1859.
3. Akelah, A.; Sherrington, D.C. *Chem. Rev*., **1981**, *81*, 557-587.
4. Gopalakrishnan, G.; Kasinath, V.; Pradeep Singh, N.D.; Thirumurugan, R.; Sundararaj, S.S.; Shanmugam, G. *Molecules,* **2000**, *5*, 845-848.
5. Curtin, D. Y.; Meislich, E.K. *J. Amer. Chem. Soc*., **1952**, *74*, 5518-5520.
6. Dulcere, J. P.; Rodriguez, J.; Santelli, M.; Zahara, J. P. *Tetrahedron Lett*., **1987**, *28*, 2009-2012.
7. Buckles, R. E.; Filler, R.; Hilfman, L. *J. Org. Chem*., **1952**, 233-242.
8. Smith, K.; James, M.; Matthews, I.; Bye, M. R. *J. Chem. Soc. Perkin Trans. 1,* **1992**, 1877-1878.
9. Cacchi, S.; Caglioti, L. *Synthesis,* **1979**, 64-66.
10. Geetha Gopalakrishnan; Pradeep Singh, N.D.; Kasinath, V.; Sivarama Krishnan, M.; Malathi, R.; Rajan,S.S. *Tetrahedron Lett*, **2001**, *42*, 6577-6579.
11. 1-Bromo-2-methoxydecane (**1a**): CA: 64:11076a, **1965**.
12. 5-(2-Bromo-1-hydroxy-1-methylethyl)-2-methylcyclohex-2-ene-1-one (**4a**): Calo,V.; Lopez,L.; Fiandanese,V.; Naso,F.; Ronzini,L. *Tetrahedron Lett*. **1978**, *49*, 4963-4966.
13. 2-Bromo-3-methoxy-2,3-dimethylbutane (**10a**): Olah, G.A.; Bollinger, J.M. *J. Amer. Chem. Soc*. **1967**, *89*, 4744-4746.
14. CCDC N°: 173576.

Sample availability: Samples of compounds **1a**, **2a**, **4a**, **6a**, **7a**, **8a**, **9a** and **10a** are available from the authors