

# King Saud University

# Arabian Journal of Chemistry

www.ksu.edu.sa



www.sciencedirect.com

# **ORIGINAL ARTICLE**



# Solid supported reagents for effecting selective transformation in natural products

V.P. Santhanakrishnan<sup>a</sup>, R. Mohankumar<sup>b</sup>, S. Narasimhan<sup>b,\*</sup>

<sup>a</sup> Centre for Plant Molecular Biology & Biotechnology, TNAU, Coimbatore 641 003, India

<sup>b</sup> Asthagiri Herbal Research Foundation, 162A Perungudi Industrial Estate, Perungudi, Chennai 600 096, India

Received 16 June 2011; accepted 31 January 2012 Available online 9 February 2012

### **KEYWORDS**

N-bromoacetamide resin; Microwave; Oxidation: Tetranortriterpenoids

Abstract Polymer supported N-bromoacetamide resin can be easily prepared by the bromination of the acetamide resin and can be used for the transformation of furan ring in tetranortriterpenoids to butryolactone with excellent selectivity and in good yield in shorter time under microwave irradiation condition.

© 2012 Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

#### 1. Introduction

Application of the solid supported reagents in combinatorial synthesis has grown in recent years due to the convenient handling and easy work up procedures. They have been employed in the synthesis of Brunsvicamide A, Lamellarins (Thilo et al., 2008; Poonsakdi et al., 2005), etc. This is very essential in the semisynthetic modification of natural products. The present study demonstrates the use of the solid supported N-bromoacetamide resin for the oxidation of furan ring in tetranortriterpenoids.

E-mail address: asthagiri.herbal@gmail.com (S. Narasimhan). Peer review under responsibility of King Saud University.



## 2. Materials and Methods

Various tetranortriterpenoids like nimbin, salannin, azadiradione, nimonol, etc. were obtained in the pure form after being subjected to repeated purification by column chromatography from the oil and fruit coat of Azadirachta indica. Similarly methylangolensate is obtained from the Entandrophragm angolense.

A microwave oven (IFB-Megatron, wattage - 1100 W, power max - 750 W, voltage - 230 Hz, frequency -2450 MHz) 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 <sup>1</sup>H- and <sup>13</sup>C-NMR experiments. CDCl<sub>3</sub> was used as the solvent. Chemical shifts are given in terms of parts per million ( $\delta$  scale). IR spectra (cm<sup>-1</sup>) were recorded on a Perkin–Elmer RX1 FT-IR spectrophotometer. Precoated thin layer chromatography plates (Emerck, Germany, Keiselgel 60 F254, 0.2 mm thickness, coated on aluminum sheets) were used. Column chromatography was performed using silica gel (60-120 mesh and 230-400 mesh).

http://dx.doi.org/10.1016/j.arabjc.2012.01.006

1878-5352 © 2012 Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

<sup>\*</sup> Corresponding author. Tel.: +91 44 24967645; mobile: +91 9840064340.







Scheme 2 Oxidation of salannin using the N-bromoacetamide resin.



Scheme 3 Regeneration of the resin.

#### 3. Preparation of the resin

#### 3.1. Nitration of the polymer

To 25 g (17.5 ml) of concentrated nitric acid was added 37 g (20 ml) of concentrated sulfuric acid in portions with shaking and the mixture is kept at 0 °C. To this mixture 13 g of the polystyrene beads are added in portions of 2 g with shaking to ensure the complete mixing. The temperature is maintained at 0 °C during the addition. After complete addition the reaction mixture is allowed to stir for 30 min at room temperature. The contents are then poured into ice cold water and the resin obtained is filtered off washed several times with water to remove the acid impurities till the pH of that filtered solution is neutral. The light yellow resin is then washed with acetone and dried. The dried weight of the resin is 14.5 g.

 $\bigcirc -NO_2$ 

*IR* (KBr) cm<sup>-1</sup>: 3455, 1636, 1521, 1422, 1347, 835, 797, 706, 598

1521-NO<sub>2</sub>, 835-C-N, 797-CH, C=C

#### 3.2. Reduction of the nitro polymer

To 12.5 g of the nitrated resin 22.5 g of the graduated tin was added. To this mixture 50 ml of the concentrated hydrochloric acid is added down the condenser in portions of 7.5 ml and the contents are shaken well. If the reaction mixture boils vigorously it is made moderate by immersing it in cold water. After the addition of 50 ml of the acid the reaction mixture is heated in a boiling water bath for 45 min. The reaction mixture is then cooled and the contents are poured into the ice cold water. The resin is then filtered off. The filtered resin is taken in a beaker and washed several times with sodium hydroxide to remove the tin particles adhering to the resin. The brown color resin is again filtered off dried and weighed. The weight of the dried resin is 10 g.

*IR* (KBr) cm<sup>-1</sup>: 3451, 2924, 2360, 1629, 1518, 1449, 1345, 830, 707

3451-NH, 2924-CH, 830-C-N

#### 3.3. Acetylation of the amine polymer

To a heterogenous solution of 9 g of the resin in 5 ml of dichloromethane 5 ml of the acetic anhydride and 5 ml of pyridine were added and stirred for 24 h. To ensure the completeness of the reaction the reaction mixture is refluxed for 30 min and the resin is then filtered off washed off several times with sodium bicarbonate to remove excess acetic anhydride and then washed with dilute hydrochloric acid to remove the pyridine that is adhering to the resin. The resin is then washed several times with water and dried. The dried weight of the light brown acetamide resin is 9.8 g.

──NHCOCH<sub>3</sub>

Table 1		Plant	and	parts	from	which	the	tetranortrit	terpenoids	were isolated.
---------	--	-------	-----	-------	------	-------	-----	--------------	------------	----------------

1	1		
Plant	Part of the plant	Products	Activity
Azadirachta indica	Oil (Govindachari et al., 1995; Henderson et al., 1968; Burke et al., 1969)	Salannin, Nimbin,	Antifeedant
		Desacetyl Salannin, Desacetyl Nimbin	Insect growth regulatory
	Fruit coat	Azadiradione	Anti-inflammatory activity and analgesic activity
Entandrophragm angolense	Bark(Njar et al., 1995)	Methylangolensate	Antifeedant, antimicrobial and anti-ulcer

### 3.4. Bromination of the acetylated polymer

To the solution of 9 g of acetamide resin in 3 ml methanol at 0 °C methanolic bromine solution containing 5 ml of methanol and 3 ml of bromine is added. It is necessary to maintain 0 °C during the addition. Then to this mixture 3 ml of 10% potassium hydroxide is added and the mixture is stirred for 18 h at the same temperature 0 °C. After 18 h the solution is kept in the refrigerator for 24 h. The resin is then filtered off and washed several times with methanol; the resin is then dried and used for various oxidation reactions. The weight of the dried resin is 10.15 g.

──NBrCOCH<sub>3</sub>

**IR** (KBr) cm<sup>-1</sup>: 3566, 3448, 2925, 2852, 2360, 1636, 1520, 1448, 1384, 1343, 1017

3566-N-Br, 2925-CH<sub>3</sub>, 2852-CH, 1636-C=O.

The bromine content in the resin analyzed under microwave condition was found to be 1.605 mmol/g.

## 3.5. Typical experimental procedure

To 60 mg (0.1 m mol) of salannin in 5 ml of methanol 600 mg of the freshly prepared N-bromoacetamide resin was added and the mixture was stirred and irradiated in a modified microwave oven for 3 min followed by subsequent filtration that yielded the product and resin A. The crude product was chromatographed to yield the pure product. The resin (A) was treated with bromine in methanol/KOH to regenerate the reagent, which can be used for further reaction.

All the products were characterized with the aid of spectral data <sup>1</sup>H- and <sup>13</sup>C-NMR and MS. Antifeedant activity studies were carried out for the oxidized products of salannin and deacetyl salannin (Narasimhan et al., 2005). There was no

 Table 2
 The list of tetranortriterpenoids and their oxidized products with the corresponding yield when subjected to oxidation with N-bromoacetamide under microwave irradiation condition.





change in the product when the reaction with salannin was performed in either ethanol or aqueous-dioxane instead of methanol. In conclusion the above reagent was found to be selective in oxidizing furan ring without affecting other functionalities like epoxide, ether, conjugated double bond or isolated double bond. No other side product was obtained under these reaction conditions even if slight excess of the reagent was used for prolonged reaction times.

## 4. Results and Discussion

Salannin, a tetranortriterpenoid present in A. indica has shown to be a bio active molecule exhibiting antifeedant activity. In our study directed toward identifying the bioactive leads, functionalization of the furan ring (Geetha et al., 2000; Morgan and Javis, 1997; Geetha et al., 2002; Geetha et al., 2001) in salannin, a bioactive functional group to the corresponding lactone was attempted using available oxidizing reagents such as bromine/methanol, N-bromosuccinimide/methanol. This resulted in either multiple products or posed problems in the isolation of the desired product (Curtin and Meislich, 1952; Duclere et al., 1987) in some cases. These reagents can cleave other sensitive functionalities present in the molecule if used in slight excess. Hence an attempt was made to apply solid supported reagent for the desired selective oxidation of furan ring. Accordingly, a resin made of N-bromoacetamide was chosen for the oxidation of the furan ring in various tetranortriterpenoids. Literature reports that N-chloro acetamide has already been used for the oxidation of the alcohols (Merrifield, 1963; Leznoff, 1974; Akelah and Sherrington, 1981; Hermkens et al., 1996; Shuttle Worth et al., 1997; Corbett, 1998; Brown, 1998; Mark Bradley and Catherine Mark, 2002; Lu and Toy, 2009). The N-bromoacetamide resin was prepared from the commercially available polystyrene copolymerized with divinyl benzene (Scheme 1).

Initial oxidation of salannin with N-bromoacetamide in methanol at 0 °C resulted in the formation of salannobuty-rolactone after 50 h with only a 25% yield. Interestingly, when the reaction mixture was subjected to microwave irradiation the reaction proceeded quantitatively within 3 min yielding the desired product in an 85% yield (Scheme 2).

Hence oxidation of various furan rings containing tetranortriterpenoids obtained from different natural products containing furan ring were carried out with N-bromoacetamide resin in methanol under microwave irradiation condition. All the natural products considered for the present study gave higher yields of the corresponding butryolactone in a very short duration. Successive washing of the resin with methanol, acetonitrile and finally by treating with mild alkaline bromine solution in methanol regenerated the reagent (Scheme 3) (Tables 1 and 2).

#### 5. Conclusion

The present study indicates the oxidation of furan ring in natural products containing a plethora of functionalities with enhanced reaction rate employing unconventional reaction medium (MWI) and solid supported reagents.

#### Acknowledgments

V.P.S. thank CSIR and R.M.K. thank DBT for funding support and Spic Science Foundation for the Analytical Center facility. We gratefully acknowledge Dr. S. Swarnalakshmi for useful discussions.

#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arabjc.2012.01.006.

#### References

- Akelah, A., Sherrington, D.C., 1981. Chem. Rev. 81, 1846.
- Brown, R.C.D., 1998. J. Chem. Soc. Perkin Trans. 1, 3293.
- Burke, B.A., Chan, W.R., Mangus, K., Taylor, D.R., 1969. Tetrahedron 25, 5007.
- Corbett, J.W., 1998. Org. Prep. Proced. Int. 30, 489.
- Curtin, D.Y., Meislich, E.K., 1952. J Am. Chem. Soc. 74, 5518-5520.

- Duclere, J.P., Rodriguez, J., Santelli, M., Zahara, J.P., 1987. Tetrahedron Lett. 28, 2009–2012.
- Geetha, G., PradeepSingh, N.D., Kasinath, V., Malathi, R., Rajan, S.S., 2000. Photochem. Photobiol. 72 (4).
- Geetha, G., Pradeep Singh, N.D., Kasinath, V., 2001. Molecules 6, 551–556.
- Geetha, G., Pradeep Singh, N.D., Kasinath, V., 2002. Molecules 7, 112–119.
- Govindachari, T.R., Suresh, G., Geetha, G., 1995. J. Liquid Chromatogr 18, 3465.
- Henderson, R., Crindle, Mc., Melera, A., Overton, K.H., 1968. Tetrahedron 24, 1525.
- Hermkens, P.H., Ottenheijm, H.C., Rees, D., 1996. Tetrahedron 52, 4527.
- Leznoff, C.C., 1974. Chem. Soc. Rev. 65, 3.
- Lu, J., Toy, P.H., 2009. Chem. Rev. 109, 815-838.
- Mark Bradley, A., Catherine Mark, J.D., 2002. Chem. Rev. 102, 3275.
- Merrifield, R.B., 1963. J. Am. Chem. Soc. 85, 2149.
- Morgan, E.D., Javis, A.P., 1997. J. Chem. Ecol. 23, 2842-2860.
- Narasimhan, S., Kannan, S., Santhanakrishnan, V.P., MohanKumar, R., 2005. Fitoterapia 76, 740–743.
- Njar, V.C., Adesanwo, J.K., Raji, Y., 1995. Planta Med. 61, 91.
- Poonsakdi, P., Rachel, K.K., Somsak, R., 2005. J. Org. Chem. 70, 5119–5125.
- Shuttle Worth, S.J., Allin, S.M., Sharma, P.K., 1997. Synthesis, 1217.
- Thilo, W., Hans-Dieter, A., Herbert, W., 2008. Org. Lett. 10, 3199-3202.