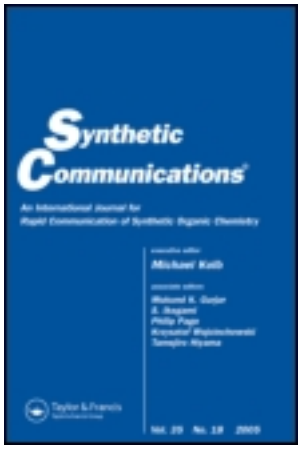

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SELECTIVE BROMINATION OF DEHYDROACETIC ACID WITH *N*-BROMOSUCCINIMIDE

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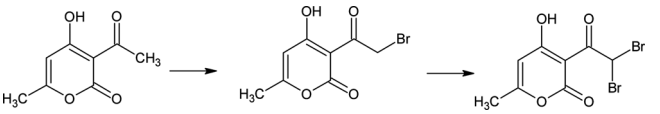
GRAPHICAL ABSTRACT



Abstract *Bromination of dehydroacetic acid has been carried out with* N*-bromosuccinimide under various conditions. The reactions led to selective bromination, thereby offering efficient synthesis of 3β-bromodehydroacetic acid (**3**), 3β,5-dibromodehydroacetic acid (**4**), 3β,3β-dibromodehydroacetic acid (**5**), and 3β,3β,5-tribromodehydroacetic acid (**6**).*

Keywords 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one; α-bromo ketones; dehydroacetic acid; α,α-dibromoketones; microwave irradiation; *N*-bromosuccinimide

INTRODUCTION

3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (dehydroacetic acid, DHA, **1**) and its derivatives[1–4] are important precursors for the synthesis of a variety of organic compounds. Investigations in the chemistry and biology of pyran-2-ones have intensified with the recognition that they are essential pharmacophores in many naturally occurring and biologically active agents. In view of these observations, efforts are continuously being made to develop efficient synthetic pathways for the synthesis of various DHA derivatives. Within this context, studies dealing with bromination of DHA are significant as the resulting brominated products such as α-bromoketones **3, 4** and α, α-dibromoketones **5, 6** (Fig. 1) are potential precursors for the synthesis of various heterocyclic compounds.

We have already reported the synthesis of pyranylthiazoles[5] of potential biological interest by reaction of **6** with various thioureas/thioamides.

The reported work on bromination[6,7] of DHA makes the use of bromine and HBr, which have several environmental problems.[8,9] Handling of liquid bromine,

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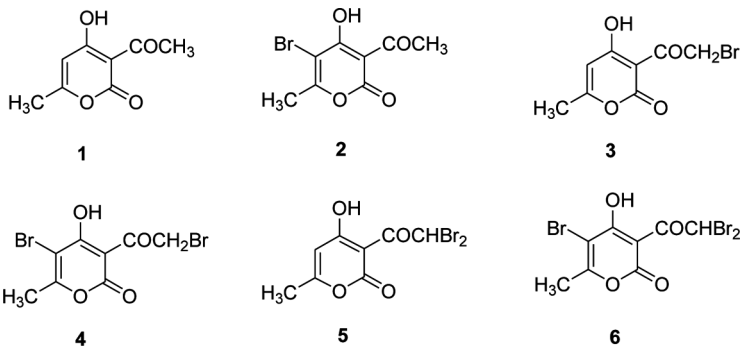


Figure 1. Different bromoderivatives of dehydroacetic acid.

because of its hazardous nature, is troublesome. To overcome these problems, alternative methods[10,11] avoiding the use of liquid bromine have been developed.

Most recent developments in this area emphasize the advantageous use of *N*-bromosuccinimide (NBS)[12–16] over Br_2 under suitable conditions, making NBS the reagent of choice for the following reasons:

1. Ease of handling
2. Selectivity of the reaction in appropriate conditions
3. Yields of the products
4. Environmental friendliness
5. Efficiency of the reaction

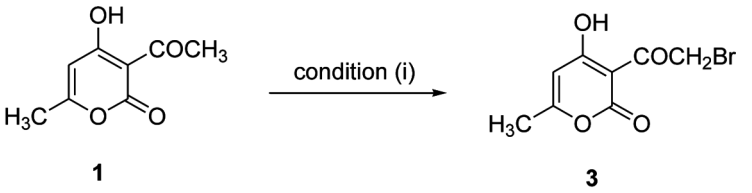
As a part of our ongoing program aimed at the development of DHA-based reactions, we now investigate the bromination of DHA using NBS. Consequently, we report here an efficient and convenient synthesis of bromo derivatives of DHA, namely 3β-bromodehydroacetic acid (**3**), 3β,5-dibromodehydroacetic acid (**4**), 3β,3β-dibromodehydroacetic acid (**5**), and 3β,3β,5-tribromodehydroacetic acid (**6**).

RESULTS AND DISCUSSION

We started our work by treatment of DHA with NBS under different sets of conditions. These reactions led to selective bromination of DHA with the formation of different products depending upon the reaction conditions. The results are discussed according to individual target molecules.

3β-Bromodehydroacetic Acid (3)

First, DHA was treated with 1 equivalent of NBS in acetonitrile under reflux. The reaction did not attain the stage of completion even after 12 h. In the course of our search for efficient methods for bromination,[17] we envisioned that the reaction could proceed efficiently by using a catalyst such as *p*-TsOH.[18] Thus, DHA was



1 3

Condition (i)- NBS/CH_3CN/*p*-TsOH

Scheme 1. Synthesis of 3β-bromodehydroacetic acid (**3**) from dehydroacetic acid (**1**).

treated with NBS in acetonitrile in the presence of *p*-TsOH under reflux. The reaction afforded the desired product **3** in 64% yield (Scheme 1).

To study the effect of the nature of protic acid on the reaction involving use of NBS in acetonitrile, variations of protic acid including trifluoroacetic acid and sulfuric acid were attempted. The complete results are summarized in Table 1.

It is clear from the results that the use of protic acids such as p-TsOH and trifluoroacetic acid (TFA) gives satisfactory results, whereas in the case of H_2SO_4 results are somewhat poorer. Although this method provides a better way for selective α-bromination,[18–20] there was scope for further improvement of yields.

In view of the encouraging recent reports[21] on the advantages of using solvent-free reaction conditions (SFRC) in bromination, we attempted the bromination of DHA under SFRC using conventional heating and microwave irradiation (Scheme 2).

The results of these experiments summarized in Table 2 reveal that the reaction occurs more efficiently in solvent-free conditions under microwave irradiation.

It is important to mention here that preparation of **3** was previously reported by Harris et al.[3] using Br_2 and HBr in 50% yield. The results of present study are superior to the reported one in terms of time, yields, and ecofriendly nature of the reagent.

3β,5-Dibromodehydroacetic Acid (4)

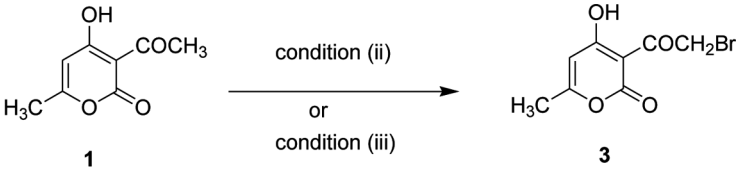
Encouraged by these results, we examined the bromination of 5-bromodehydroacetic acid using NBS under various conditions (Scheme 3).

The reaction occurred according to our expectation, leading to the regioselective synthesis of **4**. The results summarized in Table 2 again reveal that the solvent-free reaction conditions using microwave heating give the best yields.

Table 1. Effect of nature of protic acid on α-bromination of dehydroacetic acid

Reaction condition	Time (h)	Yield[a] (%)
NBS/*p*-TsOH/CH_3CN	9	64
NBS/CF_3COOH/CH_3CN	12	63
NBS/H_2SO_4/CH_3CN	16	53

[a]Yields of isolated products with regard to NBS.



1 3

Condition (ii)- NBS / *p*-TsOH / Conventional Heating

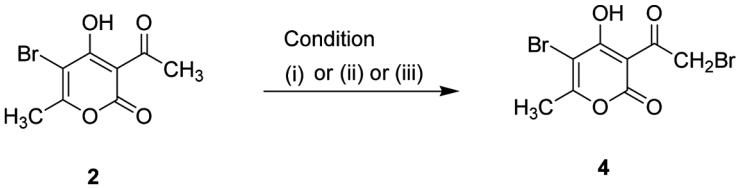
Condition (iii)- NBS/*p*-TsOH/Microwave irradiation

Scheme 2. Solvent-free synthesis of 3β-bromodehydroacetic acid (**3**) from dehydroacetic acid (**1**).

Table 2. Bromination of dehydroacetic acid under various conditions

	Reaction conditions[a]						
	Condition (i)		Condition (ii)		Condition (iii)		
Substrate	Time	Yield[b] (%)	Time	Yield[b] (%)	Time	Yield[b] (%)	Product
1	9 h	64	6.30 h	69	5 min	89	**3**
2	9.30 h	61	7.35 h	68	10 min	83	**4**
1	6.15 h	57	6.05 h	64	9 min	71	**5**
3	6 h	69	6.35 h	79	5 min	88	**5**
4	6.15 h	59	6 h	76	14 min	85	**6**

[a]Condition (i), NBS/CH_3CN/*p*-TsOH; condition (ii), NBS/*p*-TsOH/conventional heating; and condition (iii), NBS/*p*-TsOH/microwave irradiation.
[b]Yields of isolated products w.r.t NBS.



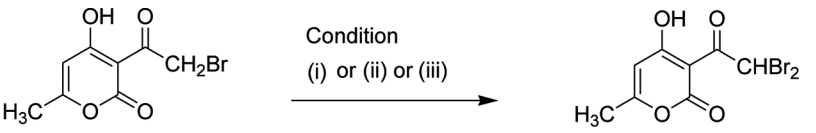
2 4

Condition (i)- NBS/CH_3CN/*p*-TsOH

Condition (ii)- NBS / *p*-TsOH / Conventional Heating

Condition (iii)- NBS/*p*-TsOH/Microwave irradiation

Scheme 3. Synthesis of 3β,5-dibromodehydroacetic acid (**4**) from 5-bromodehydroacetic acid (**2**) under different conditions.



3 5

Condition (i)- NBS/CH_3CN/*p*-TsOH

Condition (ii)- NBS / *p*-TsOH / Conventional Heating

Condition (iii)- NBS/*p*-TsOH/Microwave irradiation

Scheme 4. Synthesis of 3β,3β-dibromodehydroacetic acid (**5**) from 3β-bromodehydroacetic acid (**3**) under different conditions.

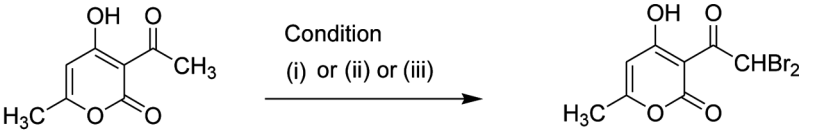
3β, 3β-Dibromodehydroacetic Acid (5)

Keeping in view the fact that the α,α-dibromo ketones can be used as a superior alternative to α-bromo ketones[22–24] in the synthesis of various heterocyclic compounds, we attempted the preparation of α,α-dibromo derivative **5** from the bromination of **3** (Scheme 4). Accordingly **3** was treated with 1.1 equivalents of NBS using *p*-TsOH in acetonitrile. The reaction afforded the desired dibromo derivative **5** in 69% yield, together with a trace amount (8%) of **4**. Interestingly, solvent-free synthesis proved to be very beneficial in obtaining **5** as pure compound in good yield.

We have also synthesized **5** directly from dehydroacetic acid by treatment with 2.5 equivalent of NBS under various conditions (Scheme 5). The results are summarized in Table 2.

3β,3β,5-Tribromodehydroacetic Acid (6)

In the light of successful results on the preparation of **3**–**5**, we finally carried out the synthesis of **6**. Tribromoderivative of DHA was prepared from **4** by treatment with NBS under different conditions (Scheme 6). All results are summarized in Table 2.



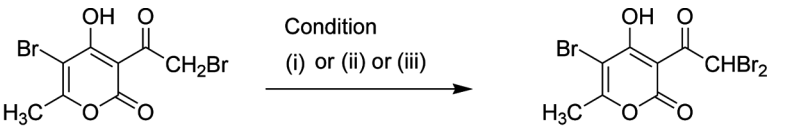
1 5

Condition (i)- NBS/CH_3CN/*p*-TsOH

Condition (ii)- NBS / *p*-TsOH / Conventional Heating

Condition (iii)- NBS/*p*-TsOH/Microwave irradiation

Scheme 5. Synthesis of 3β,3β-dibromodehydroacetic acid (**5**) from dehydroacetic acid (**1**) under different conditions.



4 6

Condition (i)- NBS/CH_3CN/*p*-TsOH

Condition (ii)- NBS / *p*-TsOH / Conventional Heating

Condition (iii)- NBS/*p*-TsOH/Microwave irradiation

Scheme 6. Synthesis of 3β,3β,5-tribromodehydroacetic acid (**6**) from 3β,5-dibromodehydroacetic acid (**4**) under different conditions.

It is worthwhile mentioning that the synthesis of α,α-dibromo ketone **6** in 68% yield has been previously reported by the action of bromine on DHA, though we have developed an alternate method using an environmentally friendly reagent (NBS) for bromination.

CONCLUSION

These results clearly indicate that NBS-mediated bromination of DHA offers a far better alternative to the existing methods involving Br_2/HBr. Further, the by-product succinimide can be readily recovered and recycled, thus making the procedure more environmentally acceptable. In particular, the solvent-free approach is remarkable in terms of simplicity, selectivity, short reaction times, and good yields of products.

EXPERIMENTAL

All reagents were purchased from commercial sources and were used without purification. Melting points were taken on slides in an electrical apparatus (Labindia visual melting-range apparatus) and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1800 Fourier transform (FT)–IR spectrophotometer. ^{1}H NMR spectra was recorded on a Bruker 300-MHz instrument using tetramethylsilane (TMS) as internal standard. Microwave-assisted reactions were carried out in a domestic microwave oven (Power Solo 17 D, 1200 W, 2450 MHz).

3β-Bromodehydroacetic Acid (3-Bromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one, 3)

NBS was slowly added (1.96 g, 11.0 mmol) to a solution of **1** (1.68 g, 10.0 mmol) and *p*-toluenesulphonic acid monohydrate (2.85 g, 15.0 mmol) in acetonitrile (20 ml) in small amounts to avoid dibromination. The mixture was stirred for 9 h under reflux. Then the solvent was reduced by distillation to half and cooled down to room temperature, and the resulting solid was dissolved in dichloromethane, washed with water, and recrystallized using ethanol to give 1.58 g (64%) of bromopyrone **3**: mp

118–120 °C (lit.[6] 118–119 °C); IR (ν_{max}, cm^{-1}, KBr): 3335, 1732, 1641; ^1H NMR ($CDCl_3$, δ): 2.33 (s, 3H), 4.71 (s, 2H), 6.03 (s, 1H), 15.6 (s, 1H).

3β,5-Dibromodehydroacetic Acid (5-Bromo-3-bromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one, 4)

NBS was slowly added (0.98 g, 5.5 mmol) to a solution containing 1.23 g (5.0 mmol) of **2** and 1.43 g (7.5 mmol) of *p*-toluenesulphonic acid monohydrate in acetonitrile (20 ml). In small amounts to avoid dibromination. The mixture was stirred for 9.30 h under reflux. Then, the reaction mixture was reduced and cooled down to room temperature, and the residue was dissolved in dichloromethane, washed with water, dried, and recrystallized using ethanol to gave 0.98 g (61%) of **4**: mp 128–130 °C (lit.[6] 129–131 °C); IR (ν_{max}, cm^{-1}, KBr): 3405, 1728, 1620; ^1H NMR ($CDCl_3$, δ): 2.54 (s, 3H), 4.72 (s, 2H).

3β,3β-Dibromodehydroacetic Acid (3,3-Dibromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one, 5)

NBS was slowly added (0.98 g, 5.5 mmol) to a solution containing (1.23 g, 5.0 mmol) of **3** and 1.43 g (7.5 mmol) of *p*-toluenesulphonic acid monohydrate in acetonitrile (20 ml). The mixture was stirred for 6 h under reflux. Then the reaction mixture was reduced and cooled down to room temperature, and the residue was dissolved in dichloromethane, washed with water, dried using anhydrous sodium sulfate, and recrystallized to afford dibromoderivative (0.98 g, 59%) of **5**: mp 84–86 °C (lit.[6] 85–86 °C); IR (ν_{max}, cm^{-1}, KBr): 3400, 1730, 1630, 1570; ^1H NMR ($CDCl_3$, δ): 2.4 (s, 3H), 7.4 (s, 1H), 6.04 (s, 1H).

3β,3β,5-Tribromodehydroacetic Acid (5-Bromo-3,3-dibromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one, 6)

NBS was slowly added (1.02 g, 5.7 mmol) to a solution containing 1.68 g (5.2 mmol) of **4** and 1.48 g (7.8 mmol) of *p*-toluenesulfonic acid monohydrate in acetonitrile (20 ml). of NBS. The mixture was stirred for 6.15 h under reflux. After that the reaction mixture was reduced and cooled down to room temperature, and the residue was dissolved in dichloromethane, washed with water, dried using anhydrous sodium sulfate, and recrystallized using ethanol to gave 1.45 g (69%) of **6**: mp 102–103 °C (lit.[7] 102–103 °C); IR (ν_{max}, cm^{-1}, KBr): 3406, 1731; ^1H NMR ($CDCl_3$, δ): 2.56 (s, 3H), 7.4 (s, 1H), 16.3 (s, 1H).

Conventionally Heated Bromination Reaction

The substrate (1.00 mmol) (**1**, **2**, **3**, or **4**), NBS (1.1 mmol), and *p*-TsOH (1.5 mmol) were taken and heated under a reflux condenser at 80–90 °C for the appropriate time as given in Table 2 for the preparation of various bromoderivatives. Then reaction mixtures were cooled to room temperature and poured into water to remove succinimide. The solid crude products were collected by decantation or filteration and dried to gave bromopyrones.

Microwave-Accelerated Bromination Reaction

The substrate (1.00 mmol) (**1**, **2**, **3**, or **4**), NBS (1.1 mmol), and *p*-TsOH (1.5 mmol) were taken, and reaction vessels were submitted to microwave irradiation for the appropriate time as shown in Table 2. Then, reaction mixtures were cooled rapidly, washed with water to remove succinimide, and recrystallized using ethanol to gave pure bromoderivatives of DHA.

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