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OPTIMIZATION AND MECHANISTIC STUDIES OF FACILE DEBROMINATION OF VINYL BROMIDES WITH VICINAL SUBSTITUTED AMINO GROUP RESIDUES

Osama I. Al-Sabbagh, Mohamed A. El-Bermawy, Mohamed A. El-Sadek and Mohamed I. Al-Ashmawi

Department of Medicinal Chemistry, Faculty of Pharmacy, Zagazig University, Egypt

ABSTRACT

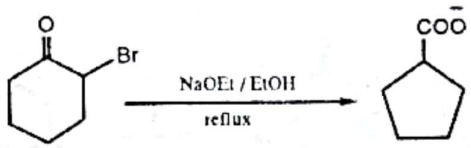
Debromination of α- bromoketones can be conducted easily. However, debromination of vinyl bromides is extremely difficult and requires vigorous conditions. This study describes the optimum conditions for the facile debromination of vinyl bromides. A plausible mechanism for the easy debromination is proposed. Also, attempted application of ring contraction of 2-bromocyclohexanediones using Favorskii conditions was unsuccessful.

INTRODUCTION

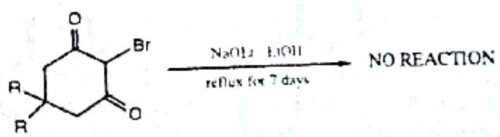
Vinyl halides are not liable to reductive debromination under normal elimination conditions[1]. They also resist nucleophilic substitution[1]. The unreactivity of vinyl halides is due to several reasons[2], for example: Sp^2 carbons are more electronegative than Sp^3 carbons. There is more attraction for electrons of Sp^2 bonds. Vinyl carbon-Br bond is shorter (d= 1.85 Å) than Sp^3-Br bond (d=1.94 Å). The leaving capacity of Br is decreased because of the resonance stabilization between the unshared pair of electrons of Br and Sp^2 in vinylic carbon i.e C-Br is stronger (vide infra).

Our main objective of this report is to develop the optimum conditions to facilitate reductive debromination and nuclophilic substitution by modification of the electron density on the carbon adjacent to the halogen atom. This could be achieved through neighboring group participation of a hetero atom e.g. oxygen or nitrogen.

It is important to mention here that α-haloketones are more reactive. For example, 2-bromocyclohexanone gives cyclopentanecarboxylic acid via intramoleular ring contraction under Favorskii conditions[3] as follows.



We applied Favorskii conditions on 2-bromo-cyclohexane- 1,3-dione **1** or 5,5-dimethyl derivative **2** (2- bromodimedone).



1: R = H
2: R = Me

The starting materials **1** and **2** were quantitatively recovered even after heating under reflux for 7 days.

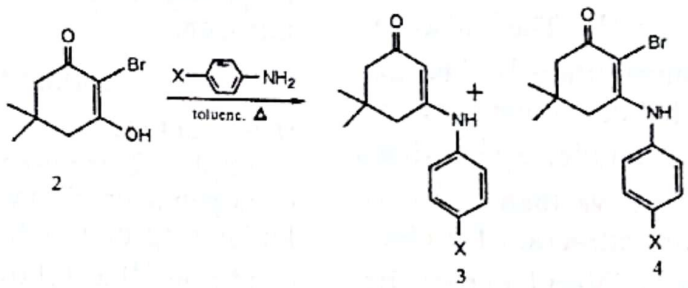
We think that compounds **1** and **2** did not undergo Favorskii rearrangements because of the shielding of C-2 which exist in the vinylic form or as enolate **1a** or **1b.** Based on this result, we

conclude that the oxygen atom of the OH is not the hetero atom of choice to facilitate debromination or nucleophilic substitution.

Astonishing observations were obtained when 2-bromodimedone **2** was heated under reflux with aromatic amines in toluene as solvent. A mixture of two enamines were isolated. One enamine **3** did not contain the Br. The other **4** was the brominated one.

The structure of enamine **3** was established by using proton nuclear magnetic resonance (^{1}HNMR). Also, its physical data matched that published in literature (4). Unambiguous synthesis of this enamine was also conducted to confrim its structure.

The debromination could be explained due to the presence of the vicinal nitrogen atom behaving as a participating neighboring group. The aromatic amine e.g. aniline, behaves as a catalizing base even though it is a weak base. Based on these results, we suggest that the presence of the nitrogen or any hetero atom that has similar characteristics is



Scheme 1

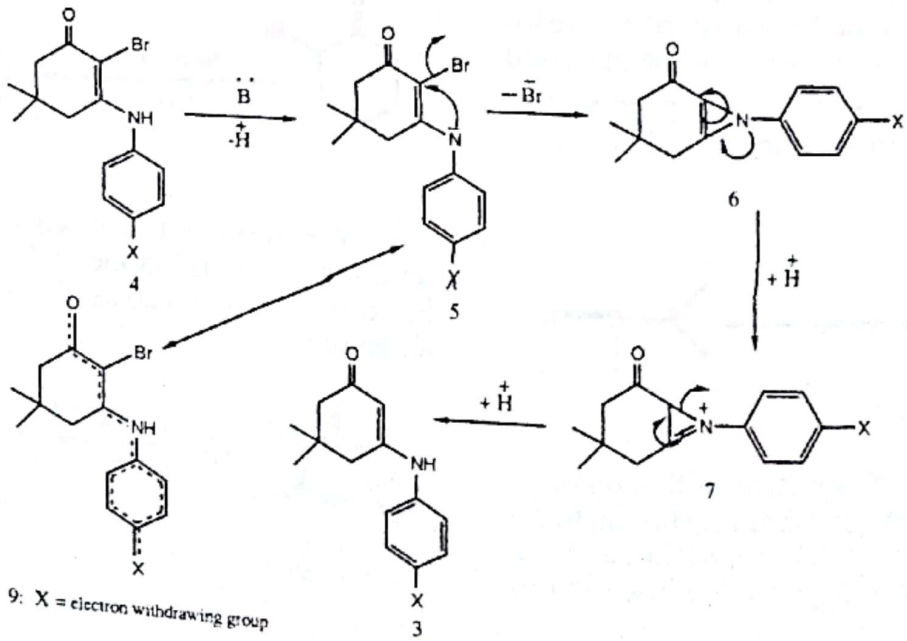
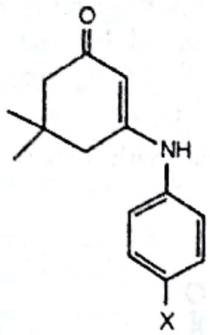


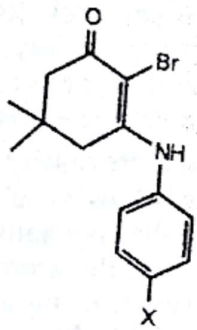
Table (1) : Physicochemical data of enaminone derivative.



Comp.	X	RS[1]	mp °C	% yield
3 a	H	Toluene	182-184	82
3 b	4-OMe	Toluene	177-179	85
3 c	4-Me	Toluene	207-209	83
3 d	4- Br	aq. EtOH	221-223	95
3 e	4-COOH	aq. EtOH	309-311	68
3 f	2- Me	Toluene	141-143	73
3 g	2- OMe	Toluene	144-146	77
3 h	c.hexyl [2]	Toluene	160-162	85
3 i	Benzyl[3]	Toluene	180-182	75

1 RS : Recrystallization Solvent
2 Cyclohexyl attached to NH
3 Benzyl attached to NH

Table (2) : Physicochemical data of bromo-enaminone derivatives and their debromination time.



Comp.	X[1]	mp °C	% yield	Time*
4 a	H	152-154	88	85
4 b	4-OMe	136-137	85	40
4 c	4-Me	144-146	86	20
4 d	4- Br	183-184	95	50
4 e	4 COOH	203-205	82	120
4 f	2- Me	146-148	80	30
4 g	2- OMe	121-123	87	45
4 h	c.hexyl[2]	145-147	84	55
4 i	Benzyl[3]	185-187	86	80

1 All compounds were recrystallized from EtOH
2 Cyclohexyl is attached to NH
3 Benzyl is attached to NH
* Time of debromination, minutes.

crucial for nucleophilic substitution and reductive elimination. We suggest the nitrogen atom which is less electronegative and more nucleophilic than the oxygen atom. Hence, it attacks C-2 to form an aziridinium intermediate **6** (Scheme 1). We suggest the following mechanism for the debromination process (Scheme 1).

The base formed an anion **5** which may form the azabicyclo derivative **6**. The aziridine **6** could undergo ring disclosure to form the enamine **3**.

To further explore the suggested mechanism, we examined two variables :

1. Various substituted bromoenamines using groups that produce different electronic effects on the phenyl ring. Consequently, the nucleophilicity of the nirtogen atom will be changed.
2. Wide range of bases were used such as NaOH, NaOEt, Na_2CO_3 and sodium acetate. Change in substituents significantly affected the rate of debromination (Table 2).

Strong bases such as NaOEt and NaOH gave the debrominated enamine **3** in less than five min. Sodium carbonate which is a very mild base was the base of choice to measure the rate of elimination.

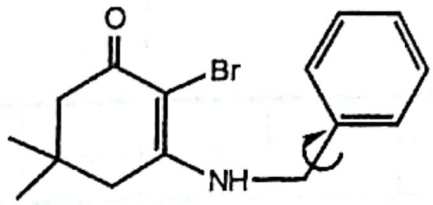
Sodium carbonate gave us a chance to follow up the reaction time.

The various substituted bromoenamines (**4**) were synthesized as follows. Heating 3,3-dimethylcyclohexane-1,3-dione (dimedone) at reflux with the appropriate amines using toluene as solvent provided the enamine derivative (**3**) in better yields than previously reproted [6-8]. Bromination of **3** using chloroform as solvent gave 2-bromoenamines (**4a-4i**). No bromination at the aromatic nucleus occurred. However, using acetic acid as solvent could lead to bromination at the aromatic ring.

The debromination time of the various 2-bromoenamine derivatives (**4a-4i**) was measured in EtOH as solvent using sodium carbonate as a moderate base. The time was monitored by TLC every five minutes starting from refluxing the reaction mixture in EtOH.

The results indicated that electron activating groups such as methyl gave the fastest elimination rate. Debromination of the 4-methyl analogue (**4c**) took place after only 20 min.

In the case of 4-methoxy derivative (**4b**), debromination occurred after 40 min. The hyperconjugation effect of the three protons of the methyl group enhanced the activation of the phenyl ring. As a result, the nucleophilicity of the nitrogen is increased. The same groups at the 2-position of the phenyl ring (compounds **4f** and **4g**) also enhanced the debromination of bromoenamines. The time of reductive elimination in **4f** and **4g** were 30 min and 45 min, respectively. Their debromination process took more time than the corresponding 4-substituted derivatives (**4b** and **4c**) we believe that the main reason is the steric interference caused by the ortho-substituents. This decrease the availability of the unshared pair of electrons of the nitrogen atom. The 4-Br derivative **4d** showed a debromination time of 50 min i.e. more than the unsubstituted analogue **4a**. The non aromatic compound **4h** showed better results than the aromatic analogue (**4a**) because of the mesomeric effect of the phenyl ring. The benzyl derivative **4i** did not increase the debromination process (time =86 min.). This may be due to the steric hindrance caused by the free rotation around the $NH-CH_2$ sigma bond. This rotation may decrease the nucleophility of the nitrogen (vide Infra).



The electron withdrawing group (COOH) as in compound **4e** showed the slowest process of debromination. The non brominated enamine **3e** was detected after 120 min. The reason may be due to the decrease of the nucleophilicity of the nitrogen atom. This may delay the formation fo the aziridine intermediate **6**. Also, the electron deactivating group may increase resonance stabilization as shown in intermediate **9** which might prefer to exist for a long time in solution. The additional resonance stabilization caused by the carboxylic group could prolong the half-life of intermediate **9**.

EXPERIMENTAL

Melting points were determined on Electrothemal Digital melting point apparatus and were uncorrected. ^{1}HNMR spectra were conducted on a varian EM 90 MHz spectrometer using TMS as internal standard. Spectral data were consistent with the assigned structures.

General method for the synthesis of enaminones (3a - 3i) :

Equimolar amount of diamedone and the appropriate primary amine were

heated at reflux in toluene for 4 h. The reaction mixture was concentrated, only 50% of the solvent was evaporated. The remaining solution was allowed to cool at room temprature. The formed precipitant was collected by filtration and recrystallized from the suitable solvent (Table 1).

General method for the synthesis of 2-bromoenamino derivatives (4a - 4i) :

The enaminone (3) was dissolved in the least amount of $CHCl_3$. An equivalent amount of $Br_2/CHCl_3$ was added dropwise to the enamine solution. The mixture was allowed to stir at room temperature for 1h then diluted with petroleum-ether until a solid was formed. The precipitate was fillered, washed with petroleum ether and recrystallized from EtOH (Table 2).

Monitoring the debromination process of 2-bromoenaminones (4a-4i) :

The bromoenamines 4 (1 mmol) was dissolved in absolute EtOH (15 ml) and mixed with equimolar amount of sodium carbonate. The mixture was heated under reflux and monitored by thin layer chromatography every five minutes using ethyl acetate-petroleum ether (3 : 2) as eluent (Table 2).

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دراسة الميكانيكية والظروف الملائمة اللازمة لتسهيل إختزال بروميدات الفينيل والتى تحمل فى تركيبها مجموعات امينية مجاورة

أسامة إبراهيم الصباغ - محمد عبد الشافى البرماوى

محمد الحسينى الصادق - محمد إبراهيم العشماوى

قسم الكيمياء الطبية-كلية الصيدلة-جامعة الزقازيق-مصر

قد أمكن فى هذا البحث التوصل الى الظروف الملائمة لإختزال بروميدات الفينيل بسهولة والمعروف أن إختزال هذه المركبات صعب جدا ويحتاج الى ظروف كيميائية غير عادية وقد تم كذلك وضع الأسس الميكانيكية لتوضيح عملية الإختزال، كذلك تم معالجة مركب ٢-برومو-١ ، ٣-ثنائي كيتو الهكسان الحلقى تحت نفس الظروف المستخدمة فى تفاعل فافورسكى ولكنها لم تتم وذلك لأسباب تم مناقشتها فى هذا البحث.