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Unprecedented dual reactivity of anhydrous potassium hydroxide in cascade cyclopropannelation/Haller–Bauer-scission/Grob-fragmentation reactions

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Dedicated to Professor Carmen Najera on the occasion of her 60th birthday with great appreciation

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ABSTRACT

We report an unprecedented type of reactivity of 'anhydrous potassium hydroxide' ('APH') in which it plays, over a large variety of related educts, sequentially the role of base and nucleophile. Some insight into the structure of reactive species as well as comparative reactivity of related reagents prepared by fusion of commercially available potassium hydroxide or by adding stoichiometric amount of water to potassium hydride is provided.

Cyclopentanones fused to a cyclopropane in α′,β′-positions and bearing a *gem*-dimethyl group in α-position and an *exo*-halogen in β-position **2** (X = Cl or Br) proved to be valuable precursors of vinyl cyclopropane carboxylic acids **1**, especially *cis*-chrysanthemic acid **1a**, on reaction with potassium hydroxide (KOH, aq DMSO, 70 °C, 4 h, Condition A;[1,2] *t*-BuOK and H_2O (3–1), 20 °C, <1 h, THF, Condition B;[1b,2] DMSO, Condition C;[1b,2] Scheme 1, Table 1). Conditions B and C which involve 'anhydrous potassium hydroxide' proved to be the most efficient owing to the particularly high nucleophilicity of this reagent.[3]

Bicyclo [3.1.0] cyclopentanones **2** have been in turn prepared from 3,4-dihalogenocyclohexanones **3′** (X, Y = Cl, Br)[1] or the related 3-halogeno-4-mesyloxy cyclohexanones **3″** (X = halogen, Y = mesyloxy)[4] and a base such as LDA[1,5] or potassium hydroxide (Condition A).[1] The latter conditions proved to be successful with **3a′** and directly lead to *cis*-chrysanthemic acid **1a** after acid work-up.[1] It involves an exceptional tandem cyclopropannelation/Haller–Bauer-scission/Grob-fragmentation reaction which unfortunately proved to be limited to **3a′** since the related **3c′** and **3d′** instead lead to the vinyl lactones **4c**/**4b** (87/13 mixture of stereoisomers) and **4d** (Scheme 1, Table 1, Condition A).[1]

We rationalized[1] those results by assuming that potassium hydroxide acts primarily with **3′** as a base (Scheme 2, entry a) or as a nucleophile (Scheme 2, entry b) to produce **1** or **4**, respectively.

We did not however explain why the absence of one or two methyl groups at C-5 affects the behavior of potassium hydroxide toward **3′**. We did not also provide a general solution to transform all the members of **3′** to **1**. This is in fact the purpose of this Letter.

In a subsequent work, we found that not only the number of substituents at C-5 but also the stereochemistry there affect the nature of the products formed on reaction with potassium hydroxide (Condition A). Thus, whereas $\mathbf{3c'_{Br}}$ produces lactones (Table 1, entry 4), its epimer at C-5 $\mathbf{3b'_{Br}}$ leads under similar conditions to the same mixture of the lactones **4c/4b** (87/13) and a single stereoisomer of **1b** in which the latter prevails (Scheme 1, Table 1, Condition A, entry 3 compare to entry 4).

We were rather surprised to find that the related 3-bromo-4-mesyloxy cyclohexanone $\mathbf{3a''_{Br}}$[4] does not behave as the related dibromide $\mathbf{3a'_{Br}}$[1] which also bears the two geminal methyl groups at C-5. It mainly leads to a mixture of chrysanthemic acid **1a** and its isomeric chrysanthemolactone **4a** in which the latter prevails (**4a**/**1a**: 2/1, Scheme 1, Table 1 entry 7, Condition A). We also observed that the percentage of lactone increases substantially by carrying out the reaction at 20 °C instead of 70 °C (**4a**/**1a**: 9/1, Scheme 1, Table 1 entry 7, Condition A). Furthermore, whereas 3-iodo-4-mesyloxy cyclohexanone $\mathbf{3a''_{I}}$[4] nearly exclusively generates

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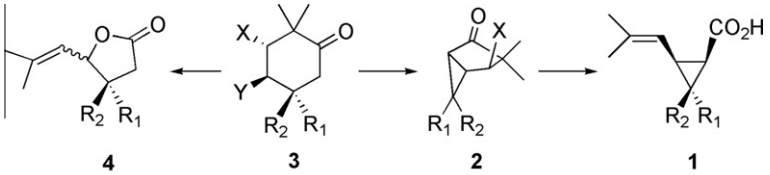
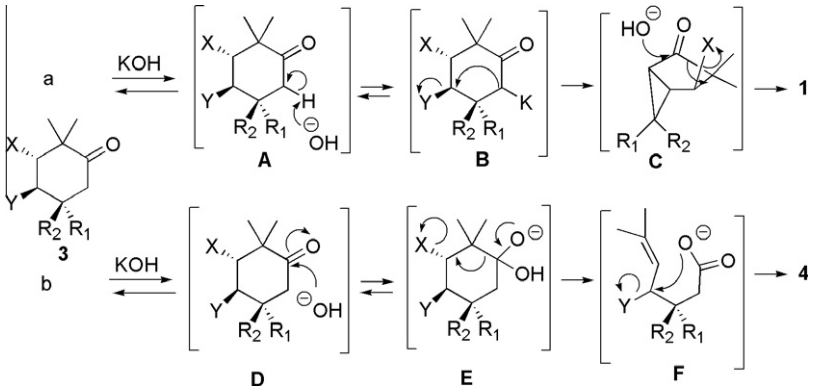


Scheme 1.



Scheme 2.

chrysanthemolactone **4a** (Scheme 1, Table 1 entry 8 Condition A), its chloro analogue $\mathbf{3a''_{Cl}}$[4] exclusively produces chrysanthemic acid **1a** (Scheme 1, Table 1 entry 6, Condition A, compare to entries 7 and 8). In the latter case, the bicylic [3.1.0] β-chloroketone[1b] intermediate $\mathbf{2a_{Cl}}$ has been trapped if the reaction is carried out at 20 °C instead of 70 °C (20 °C, 1 h, 70%).

We envisage that the nature of the products **1** or/and **4** formed (Scheme 2) could be related to the subtile stereoelectronic effects as well as to the nature of the leaving groups at C-3 and C-4 on **3**. We have ascertained using X-ray crystallography that $\mathbf{3a'_{Br}}$ and $\mathbf{3c'_{Br}}$ possess a chair conformation with the halogens and mesyloxy group lying in equatorial position as disclosed in Figure 1.

Similar results have also been observed for $\mathbf{3d'_{Br}}$, $\mathbf{3a''_{Br}}$ and $\mathbf{3a''_{I}}$.

The attack of hydroxyl anion can take place on the C-6 hydrogens or on the carbonyl carbon of **3**. We assume that:

(i) Metalation of **3** is best achieved on the more acidic C-6 Ha. It should provide, under kinetic control, the corresponding enolate **Ba** by constant overlap of the orbitals involved (Scheme 3, entry a).[6] Metalation of He, however, the less acidic of the two hydrogens attached to C-6, achieves the antiperiplanar arrangement of atoms and bonds suitable for the cyclization leading to cyclopropane ring (Scheme 3, entry b) and therefore successful cyclization is expected to involve an equilibrium.[7]

(ii) Addition of the hydroxide ion onto the carbonyl carbon[8] from the top-face generates the intermediate **Ea** whose alkoxide ion is adequately positioned to favor a fragmentation reaction in which the atoms and bonds are localized in an antiperiplanar conformation[9,10] leading to the open chain intermediate **F** precursor of the vinyl lactones **4** (Scheme 4,

Table 1
Reactivity of 2,2-dimethylcyclohexanones **3** toward KOH and *t*-BuOK–H_2O

Entry	**N**	R_1	R_2	X	Y	Condition A: KOH, aq DMSO **1**/**4** yield % (**1**/**4** ratio) [*T* (°C), *t* (h)][a]	Condition B: *t*-BuOK–H_2O, THF **1**/**4** (yield %) (**1**/**4** ratio) [*T* (°C), *t* (h)][a]	Condition C: *t*-BuOK–H_2O, DMSO **1**/**4** (yield %) (**1**/**4** ratio) [*T* (°C), *t* (h)][a]
1	$\mathbf{3a'_{Cl}}$	Me	Me	Cl	Cl	64/0 (100/0) [70, 4][1]	80/0 (100/0) [20, 1]	
2	$\mathbf{3a'_{Br}}$	Me	Me	Br	Br	86/0 (100/0) [70, 2][1]	94/0 (100/0) [20, 0.4]	65/0 (100/0) [20, 0.5]
3	$\mathbf{3b'_{Br}}$	H	Me	Br	Br	65/7 (76/24) [70, 1]	94/0 (100/0) [20, 0.4]	
4	$\mathbf{3c'_{Br}}$	Me	H	Br	Br	0/81 (0/100) [70, 2][1]	92/0 (100/0) [20, 0.4]	
5	$\mathbf{3d'_{Br}}$	H	H	Br	Br	0/65 (0/100) [70, 2][1]	86/0 (100/0) [20, 0.4]	
6	$\mathbf{3a''_{Cl}}$	Me	Me	Cl	Ms	57/0 (100/0) [70, 6][b]	72/0 (100/0) [20, 0.6][c]	75/0 (100/0) [20, 2]
7	$\mathbf{3a''_{Br}}$	Me	Me	Br	Ms	26/53 (33/67) [70, 1] 7/61 (10/90) [20, 8]	89/0 (100/0) [20, 0.6]	76[d]/5 (94/6) [20, 2]
8	$\mathbf{3a''_{I}}$	Me	Me	I	Ms	7/66 (10/90) [70, 1] 4/67 (5/95) [20, 3]	89/4 (96/4) [20, 0.6]	36[e]/5 (88/12) [20, 2]

[a] The yields disclosed refer to that of isolated, analytically pure compounds as single stereoisomer for **1** and as a mixture of stereoisomers for **4** unless otherwise stated.
[b] 6% of β-chloroketone $\mathbf{2a_{Cl}}$ also recovered.
[c] 18% of β-chloroketone $\mathbf{2a_{Cl}}$ also recovered.
[d] Chrysanthemic acid **1a** proved to be a *cis*/*trans*-mixture of isomers 83/17.
[e] Chrysanthemic acid **1a** proved to be a *cis*/*trans*-mixture of isomers 30/70.

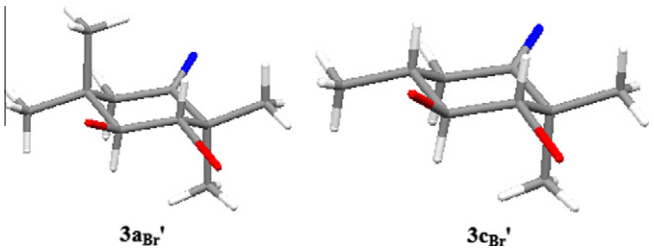
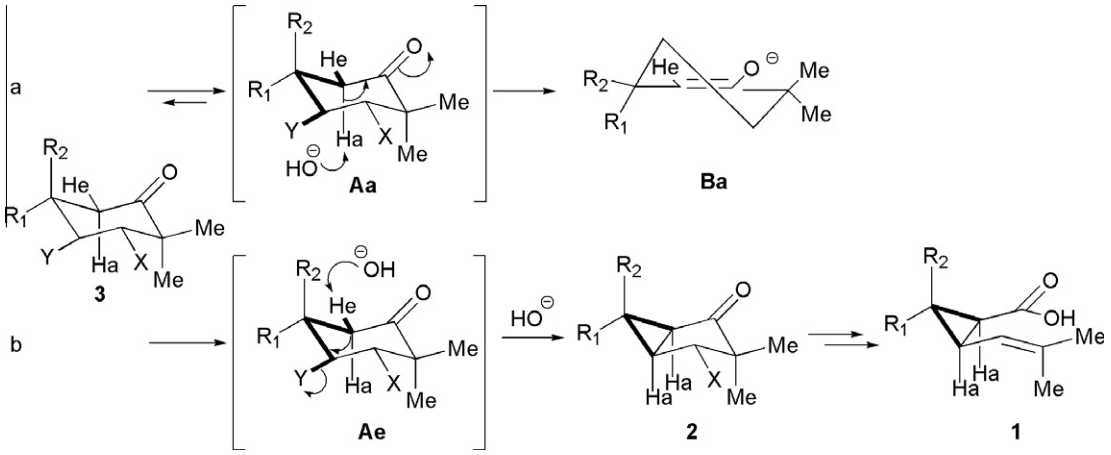


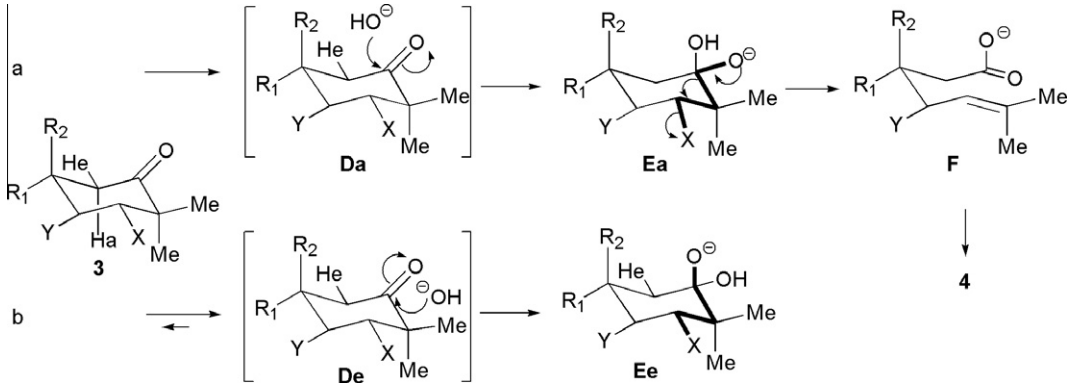
Figure 1.

entry a). This approach could be hampered with a bulky R_2 group (1,3-diaxal interaction). Addition from the bottom-face however provides instead **Ee** whose fragmentation is much less favored (Scheme 4, entry b).

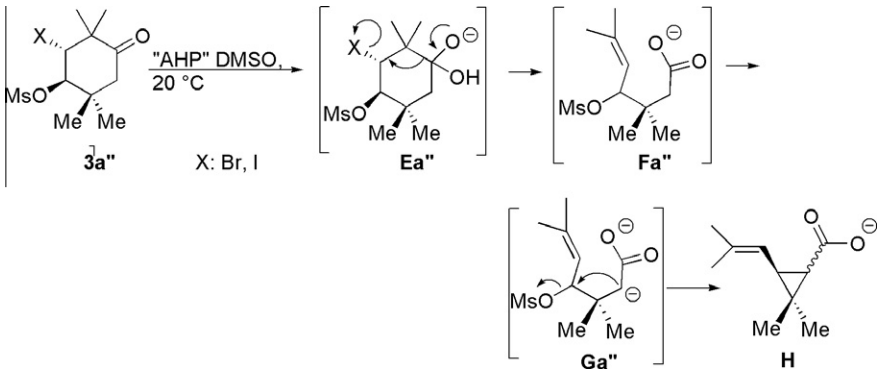
However, the electronic factors are not the only ones which could play an important role in the process. It was found that the relative leaving group ability of X and Y on **3** plays also a crucial role since the better leaving group favors the process in which it is involved favoring thus the formation of either **1** or **4**.



Scheme 3.



Scheme 4.



Scheme 5.

Thus vinyl cyclopropane carboxylic acids **1** are obtained from compounds $\mathbf{3a'_{Cl}}$, $\mathbf{3a'_{Br}}$, $\mathbf{3b'_{Br}}$, $\mathbf{3a''_{Cl}}$ which possess an axial methyl group (R_2 = Me) at C-5 and a leaving group at C-4 with similar or better leaving group aptitude than at C-3 (see Scheme 4, entry a; Table 1, entries 1–3 and 6; Condition A). The higher percentage of cyclopropane derivative **1** from compounds $\mathbf{3a'_{Cl}}$, $\mathbf{3a'_{Br}}$, $\mathbf{3a''_{Cl}}$ bearing a *gem*-dimethyl groups at C-5 over $\mathbf{3b'_{Br}}$ missing it may be rationalized by involving the Thorpe-Ingold effect (Table 1 compare entry 3 to entries 1 and 2; Condition A).[11]

It is interesting to note that the vinyl lactones **4** are mainly produced from (i) $\mathbf{3c'_{Br}}$ and $\mathbf{3d'_{Br}}$ which miss the axial methyl group even if the leaving groups at C-3 and C-4 are the same (Table 1, entries 4 and 5; Condition A) or (ii) $\mathbf{3a''_{Br}}$ or $\mathbf{3a''_{I}}$ which possess an axial methyl group at C-5 but bear a better leaving group at C-3 than at C-4 (Table 1, entries 7 and 8; Condition A).

In order to promote the one-pot synthesis of vinyl cyclopropane carboxylic acids **1** from the cyclohexanones **3** that we were unable to achieve using potassium hydroxide under condition A, we decided to use 'anhydrous potassium hydroxide' ('APH') instead.[2,3]

'APH' is a 2/1 mixture of potassium *t*-butoxide and potassium hydroxide and we expected that the former reagent would act as a powerful base[12] to generate the cyclopropane ring whereas the naked hydroxide anion would achieve, in a second step, the fragmentation reaction producing after acidic treatment the vinyl cyclopropane carboxylic acid **1**. This was quite risky since, except in one case,[13] 'APH' has been used as a powerful nucleophile.[2,3] It has been successfully used to transform, in high yields and under mild conditions (ether, 20 °C, few hours), even sterically hindered esters,[3] tertiary amides,[3b] and non-enolizable ketones[1b,2,3] to the corresponding potassium carboxylates and potassium alcoholates, -amides or -carbanions, respectively (Scheme 1), without epimerizing their α-carbon.

The reaction of 'APH' on **3** is best achieved in THF using a reactant/reagent ratio (**3**/*t*-BuOK/H_2O: 1/7.6/2.3) in which it delivers in very high yield the *cis*-vinyl cyclopropane carboxylic acids **1** at 20 °C (Table 1, Condition B). The reaction proved to be stereospecific delivering a different stereoisomer of desmethyl *cis*-chrysanthemic acids **1b** and **1c** from each stereoisomers of 3,4-dibromo-2,2,5-trimethylcyclohexanones $\mathbf{3b'_{Br}}$ and $\mathbf{3c'_{Br}}$ used (Table 1, entries 3 and 4; Condition B).

Performing the reaction in DMSO does not offer advantages, it is often slower and produces diastereoisomeric mixtures of *cis*- and *trans*-chrysanthemic acid **1a** from 3-bromo- $\mathbf{3a''_{Br}}$ and 3-iodo- $\mathbf{3a''_{I}}$ 4-mesyloxy-2,2,5,5-tetrametylcyclohexanones (Table 1, Condition C, ***cis*-1a**/***trans*-1a**: 83/17 from $\mathbf{3a''_{Br}}$ and 30/70 from $\mathbf{3a''_{I}}$", compare to Conditions A and B).

We have been unable to find the origin of the *trans*-chrysanthemic acid **1a** formed in this process. We have however secured, by independent reactions, that 'AHP' in DMSO (Condition C) is unable to (i) epimerize potassium *cis*- to *trans*-chrysanthemate or (ii) to transform the lactone **4a** to **1a**. Another hypothesis which involves a completely different mechanism is presented in Scheme 5. It implies the metalation of the intermediate **Fa**″ (resulting from the attack of 'APH' on the carbonyl group of **3a**″) followed by cyclization through **Ga**″.

In order to have a better insight in the real species required for successful synthesis of chrysanthemic acid **1** we have carried out the reaction of 3-bromo-4-mesyloxy-cyclohexanone $\mathbf{3a''_{Br}}$ with potassium hydroxide generated by (i) dehydration, on heating, of powdered commercial potassium hydroxide or (ii) on reacting stoichiometric amounts of water on potassium hydride (1 equiv KH, 1 equiv H_2O, THF, 20 °C).[3,14] Those reagents miss potassium *t*-butoxide as well as *t*-butanol.

We found that both reactions carried out in THF at 20 °C are slower (18 h and 66 h, respectively) than those involving 'APH' (0.5 h). Using dried KOH, the bicyclo [3.1.0] beta-bromo cyclopentanone $\mathbf{2a_{Br}}$ (70%) and the vinyl lactone **4a** (30%) are formed whereas using KOH generated from potassium hydride, the bicyclo [3.1.0] beta-bromo cyclopentanone $\mathbf{2a_{Br}}$ (19%) and *cis*-chrysanthemic acid **1a** (81%) are instead produced.

Dried KOH in THF behaves as KOH in aq DMSO (Condition C). KOH from KH behaves as 'AHP' in chemoselectivity but not in reactivity. 'AHP' therefore possesses an exceptional reactivity which differentiates it from the two 'anhydrous potassium hydroxide' and wet potassium hydroxide reagents tested in this study.

The results reported are far beyond the scope of the multistep one-pot transformation we have finally successfully achieved using 'APH'. They suggest that potassium *t*-butoxide and *t*-butanol which are also present in 'APH' play a crucial role in its reactivity. They also extend the scope of action of this exceptional reagent far beyond what has been already published.[3e]

General procedure for the 'one-pot' cyclization–fragmentation reactions

With 'AHP' in THF: water (21 mg, 1.15 mmol) is added at 20 °C to a solution of freshly sublimed potassium *tert*-butoxide (426 mg, 3.8 mmol) in dry THF (4 mL) and the reaction mixture is stirred for 0.25 h at that temperature. A solution of 3-bromo-4-mesyloxy-2,2,5,5-tetramethyl-cyclohexanone $\mathbf{2a''_{Br}}$ (164 mg, 0.5 mmol) in dry THF (2 mL) is then added dropwise at 20 °C. The reaction is monitored by TLC (pentane/diethyl ether 80:20) and the reaction is quenched by icy water (5 mL) after 0.6 h. Aqueous HCl (10%) is then added (until pH 2) and the solution is extracted with ether (4 × 10 mL). The combined organic extracts are washed with water (2 × 3 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography using pentane/diethyl ether (60:40) as eluent to furnish 75 mg (89%) of **1a**.

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