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Epoxyisophorone ring-opening: an efficient route for the introduction of functional groups at position 2 of isophorone

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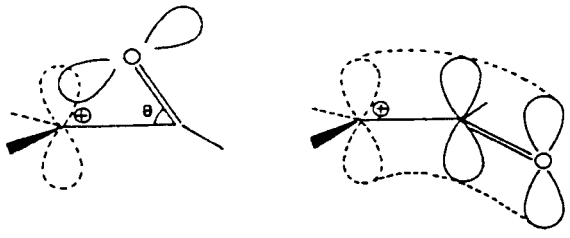
Abstract—Functional groups were selectively introduced at the C-2 position of isophorone via the epoxide ring-opening with several nucleophiles. Various behaviours were observed depending on the reaction conditions and the nature of nucleophilic reagents. Electronic and steric effects of the reactants were discussed. The best experimental systems involved $LiClO_4$ salt effect in acetonitrile, phase transfer catalysis or KF–alumina under solvent-free conditions under microwaves.

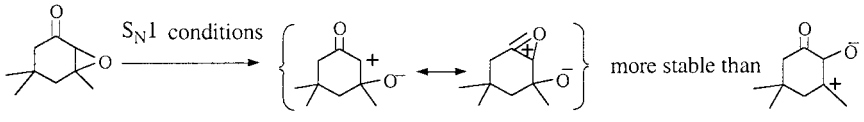
Ring-opening of epoxyisophorone is a very selective reaction, only occuring at α-position (C_2).[1–6] On one hand, this position is the less hindered site, consequently prone to lead to S_N2 ring opening. On the other hand, the more stabilized carbocation (obtained under S_N1 conditions) is an α-acylcarbenium ion (Scheme 1) stabilized by overlapping between the 2p vacant orbital of the carbocation and the occupied lone pair of oxygen or the π orbital of the carbonyl group[7,8] (Scheme 2).

Furthermore, a conformational study of epoxyisophorone has shown that the more accessible site was at C_2 position. Some highly regio- and stereoselective additions at this carbon were previously described in accordance with the ^1H NMR spectrum.[9–11] This reaction can thus provide an useful method for building systems needing bonds formation at carbon 2 of isophorone. It could be for instance, the case for the preparation of bicyclic (carbo or heterocyclic) compounds with isophorone skeleton (either with heteroatoms or electron withdrawing groups able to generate carbanions). This reaction allows us to avoid the difficult problem of functionalization in position 2 of isophorone. In basic medium, the anion generated from isophorone is a mesomeric one (Scheme 3), able to react with an electrophile either by oxygen, C_2 or C_7 atoms[12–16] or to give dimerisation by autocondensation.[17–19]

We thus explored here the most efficient experimental conditions to promote ring-opening of epoxyisophorone by various C-nucleophiles including cyanide anion as a non-bulky linear model and a series of carbanions from activated methylenes as bulky and charge delocalised species.



Scheme 2. (From ref. 7).



Scheme 1.

Keywords: epoxide ring-opening; isophorone; microwave irradiation; phase transfer catalysis; solvent-free conditions.
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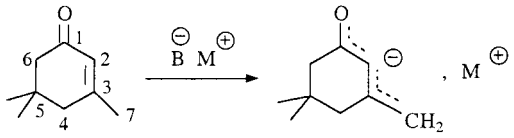
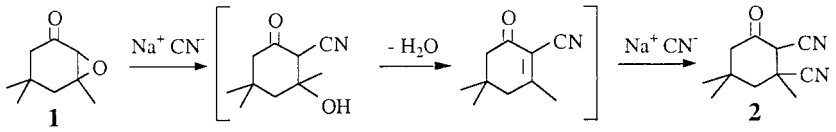


Scheme 3.



Scheme 4.

Table 1. Epoxyisophorone ring-opening with cyanide ion (NaCN: 2 equiv.)

Solvent	Additive	Temperature (°C)	Time	Yield (%) **2**[a]
CH_3CN	–	20	12 h	58
CH_3CN	*$LiClO_4$ (1 equiv.)*	*20*	*12 h*	*95*
CH_3CN	$LiClO_4$ (1 equiv.)	20	1 h	90
CH_3CN	Aliquat (5%)	20	12 h	86
–	Aliquat (5%) (Δ)	95	1 min	60
–	Aliquat (5%) (MW dom)	95[b]	1 min	90
–	*Aliquat (5%) (MW mon)*	*95*	*1 min*	*94*
–	Alumina (Δ)	86	2 min	53
–	Alumina (MW dom)	86[b]	2 min	86
–	*Alumina (MW mon)*	*86*	*2 min*	*92*

[a] Yield in isolated products.
[b] Final temperature was evaluated at the end of microwave irradiation.

1. Results

In order to optimise the results, different sets of reaction conditions were studied. They included reactions in protic and aprotic solvents, the effect of lithium perchlorate in aprotic medium (acetonitrile) providing electrophilic assistance by Li^+,[20] solid–liquid solvent-free phase transfer catalysis (PTC),[21,22] either by conventional heating or under microwaves,[23] reactions on solid support (alumina or KF–alumina),[24] by conventional heating or under microwaves.[25,26] In the last case, two equipments were used, either a domestic oven (MW dom) with a heterogeneous distribution of electromagnetic field, or a monomode reactor (MW mon) with focused waves,[27] and an accurate control of temperature all along the reaction by an infrared detection. To check possible specific (non purely thermal) microwave effects, yields were compared with those obtained with the same reaction performed under conventional heating (Δ) under the same conditions (vessel, time, temperature, pressure).

In Table 1, the main results obtained for NaCN opening of epoxyisophorone under several experimental conditions are summarised. The product of the reaction is a dicyanocompound **2** resulting from ring-opening on position 2, subsequent dehydration and Michael addition (Scheme 4).

When the reaction was carried out in refluxing methanol, besides compound **2** (78%), some amount of solvolysis product was formed leading to 2-methoxyisophorone (9%).[5]

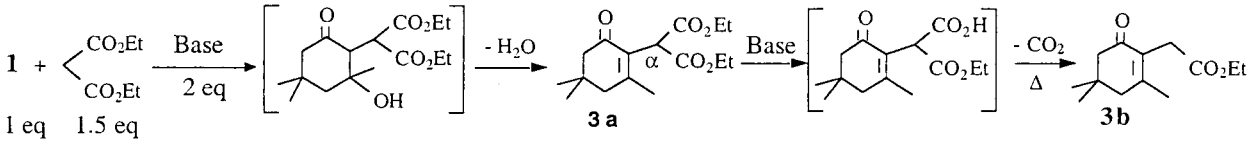
The best conditions (in italics) have been consequently selected for the reactions with the other carbanions. Depending on nature of these species, one or two products were obtained. The first ones (compounds **a**) were the 2-substituted isophorones, the second ones (compounds **b**) resulted from **a** either by a partial hydrolysis followed by decarboxylation (Scheme 5), partial hydrolysis (Schemes 6 and 7), an internal 1,4-addition (Scheme 8), a subsequent cyclisation by carbanion or amino attack on carbonyl group (internal 1,2-addition, Schemes 9 and 10). The main results are summarised in Tables 2–7.

2. Discussion

After analysis of the results summarised in the tables, we found three different types of reaction conditions leading to rather similar and high yields:

(i) the use of lithium salts in acetonitrile at room temperature. The reaction times ranged from 15 min for the epoxide ring-opening with malonitrile to 24 h with diethylmalonate and cyanoacetamide in very good yields (88–94%);
(ii) the solvent-free reactions under phase transfer catalysis (PTC) conditions in a focused microwave reactor leading to close yields in very much shorter times (89–94% within 20 s–10 min);
iii) the use of KF impregnated onto alumina in dry media under microwave with 84–92% yields within 1–10 min.

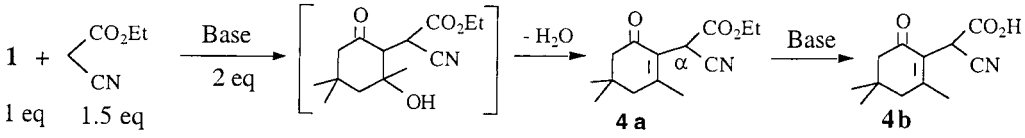
Dealing with microwave activation, either under PTC conditions or for supported reactions, an important specific (non purely thermal) MW effect is evidenced, as yields were significantly higher in the former type of activation. This specific effect can find its interpretation in terms of lowering parameters of activation due to entropic effects[28] or in high localised microscopic temperatures (hot spots).[29]



Scheme 5.

Table 2. Epoxyisophorone ring-opening with diethylmalonate

Solvent	Basic system	Temperature (°C)	Time	**3**	Yield (%)
CH_3CN	$K_2CO_3/LiClO_4$	20	24 h	**a/b** (56/44)	*88*
–	K_2CO_3/Aliquat (Δ)	95	2 min	**a/b** (53/47)	40
–	K_2CO_3/Aliquat (MW dom)	95	2 min	**a/b** (60/40)	62
–	K_2CO_3/Aliquat (MW mon)	95	10 min	**a/b** (60/40)	83
Toluene	K_2CO_3/Aliquat (MW mon)	95	10 min	**a/b** (65/45)	*92*
–	KF/Al_2O_3 (Δ)	85	10 min	**a/b** (52/48)	44
–	KF/Al_2O_3 (MW dom)	85	10 min	**a/b** (53/47)	53
–	KF/Al_2O_3 (MW mon)	85	10 min	**a/b** (55/45)	*74*



Scheme 6.

Table 3. Epoxyisophorone ring-opening with ethylcyanoacetate

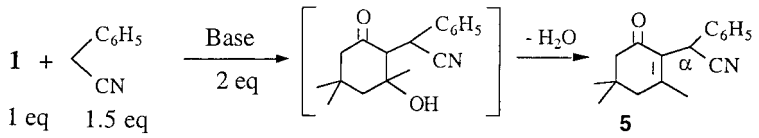
Solvent	Basic system	Temperature (°C)	Time	**4**	Yield (%)
CH_3CN	$K_2CO_3/LiClO_4$	20	30 min	**a/b** (67/33)	*90*
–	K_2CO_3/Aliquat (Δ)	70	40 s	**a/b** (80/20)	51
–	K_2CO_3/Aliquat (MW mon)	73	40 s	**a/b** (77/23)	91
–	K_2CO_3/Aliquat (MW mon)	70	1 min	**a/b** (62/38)	*90*
–	KF/Al_2O_3 (Δ)	70	10 min	**a/b** (68/32)	72
–	KF/Al_2O_3 (Δ)	73	1 min	**a/b** (81/19)	64
–	KF/Al_2O_3 (MW mon)	73	1 min	**a/b** (80/20)	*90*

One can also appreciate the higher efficiency of monomode reactors when compared to domestic ovens due to more homogeneous electric field inside the cavity and consequently to a better energetic yield. Such an observation has a lot of precedents.[30–35] In two cases (Tables 2 and 6), the presence of toluene is beneficial to the reaction in connection with dilution in a non-polar solvent (i.e. transparent to MW) and therefore prone to allow specific interactions between waves and reactants.

Whatever the conditions applied, the malononitrile anion was the most reactive nucleophile whereas the anions generated from ethylmalonate and ethylacetoacetate seemed to be the less reactive ones.

Compounds **b** were derived from products **a** according to the mechanism described in Scheme 11. Compounds **a** had various behaviours either according to their bulkiness and electronic effects or to their ability to lose a proton in basic media. Therefore, when Nu=CN, **a** gave a 1,4-intermolecular addition with another cyanide anion (compound **2**). When $Nu=CH(CN)_2$, **a** underwent a 1,4-intramolecular addition by generation of internal carbanion (compound **6**). When such species could not be generated, because of the bulkiness of Nu ($CH(CO_2Et)_2$, $NCCHCO_2Et$), partial hydrolysis and decarboxylation or hydrolysis took place giving rise to a mixture of **3a**, **b** and **4a**, **b**, respectively. When $Nu=C_6H_5CHCN$, no evolution was observed (compound **5**). A 1,2-intramolecular addition on the carbonyl group with the less hindered carbanion issued from $Nu=MeCOCHCO_2Et$ gave a carbocyclic compound **7** by a Robinson's annulation. A similar 1,2-internal condensation of the amino group in compound **8a** led to a heterocyclic product **8b**.

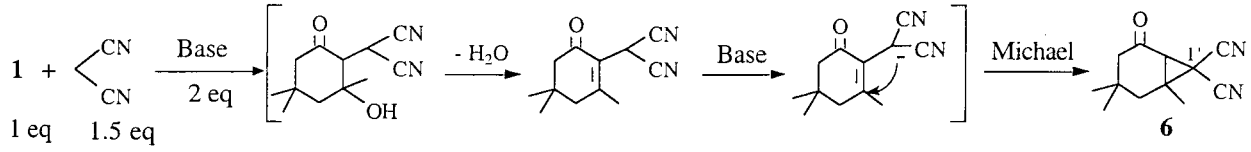
All the structures were assigned on the basis of the ^1H and ^{13}C chemical shifts and multiplicity of proton signals in ^1H NMR spectroscopy. The spectrum of **2** in $CDCl_3$ exhibited undoubled signals for each proton, indicating the presence of axial–axial and equatorial–axial stereoisomers in a 7:3 ratio. In addition, weak signals corresponding to a small amount of the enolic form were present in the spectrum, the axial–axial dicyano compound being the major isomer under these conditions (2,3-dicyano-3-methyl cyclohexanone was reported to be about 70% enolised in $CDCl_3$).[36] When the spectrum was recorded in pyridine-d_5,



Scheme 7.

Table 4. Epoxyisophorone ring-opening with phenylacetonitrile

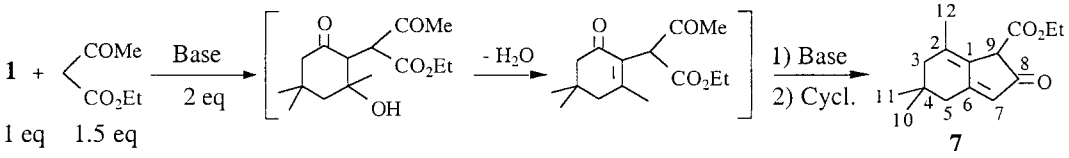
Solvent	Basic system	Temperature (°C)	Time	Yield (%) **5**
CH_3CN	$K_2CO_3/LiClO_4$	60	4 h	*90*
–	K_2CO_3/Aliquat (Δ)	105	2 min	57
–	K_2CO_3/Aliquat (Δ)	105	30 min	68
–	K_2CO_3/Aliquat (MW mon)	105	2 min	86
–	K_2CO_3/Aliquat (MW mon)	105	5 min	*89*
–	KF/Al_2O_3 (Δ)	80	2 min	48
–	KF/Al_2O_3 (MW mon)	80	2 min	*84*



Scheme 8.

Table 5. Epoxyisophorone ring-opening with malonitrile

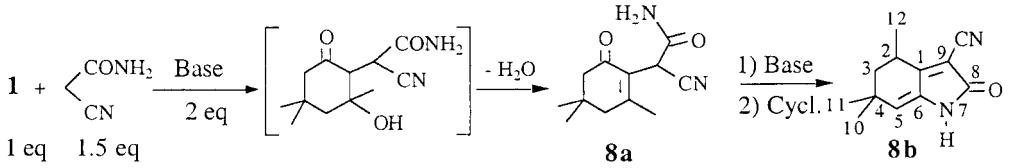
Solvent	Basic system	Temperature (°C)	Time	Yield (%) **6**
CH_3CN	$K_2CO_3/LiClO_4$	20	15 min	*94*
–	K_2CO_3/Aliquat (Δ)	58	20 s	64
–	K_2CO_3/Aliquat (MW mon)	58	20 s	*92*
–	KF/Al_2O_3 (Δ)	60	1 min	61
–	KF/Al_2O_3 (MW mon)	60	1 min	*88*



Scheme 9.

Table 6. Epoxyisophorone ring-opening with ethylacetoacetate

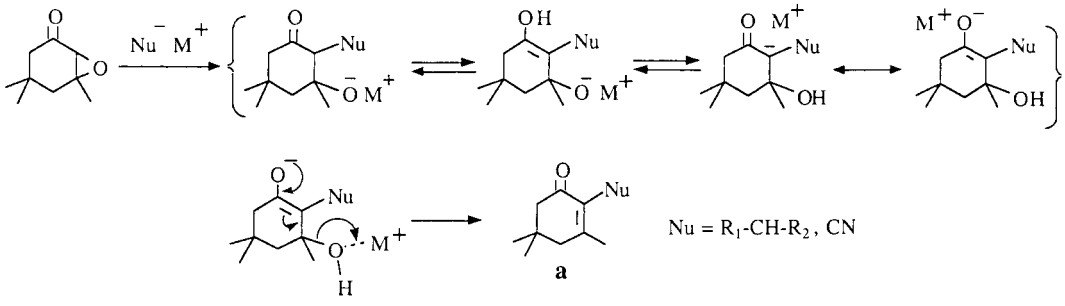
Solvent	Basic system	Temperature (°C)	Time	Yield (%) **7**
CH_3CN	$K_2CO_3/LiClO_4$	60	3 h	*90*
–	K_2CO_3/Aliquat (Δ)	85	2 min	40
–	K_2CO_3/Aliquat (MW mon)	85	2 min	78
Toluene	K_2CO_3/Aliquat (MW mon)	85	5 min	*89*
–	KF/Al_2O_3 (Δ)	86	2 min	48
–	KF/Al_2O_3 (MW mon)	86	2 min	73
–	KF/Al_2O_3 (MW mon)	86	10 min	*85*



Scheme 10.

Table 7. Epoxyisophorone ring-opening with cyanoacetamide

Solvent	Basic system	Temperature (°C)	Time	**8**	Yield (%)
CH_3CN	$K_2CO_3/LiClO_4$	20	24 h	**a/b** 39/61	*88*
–	K_2CO_3/Aliquat (Δ)	90	1 min	**a/b** 19/81	54
–	K_2CO_3/Aliquat (MW mon)	90	1 min	**a/b** 26/74	*91*
–	K_2CO_3/Aliquat (MW mon)	90	2 min	**a/b** 36/64	90
–	KF/Al_2O_3 (Δ)	80	2 min	**a/b** 21/79	60
–	KF/Al_2O_3 (MW mon)	80	2 min	**a/b** 35/65	84
–	KF/Al_2O_3 (MW mon)	80	10 min	**a/b** 45/55	*89*



Scheme 11.

keto–enolic equilibrium was entirely displaced to the enolic form. This result was also established by an infra-red study: when the product was dispersed in KBr, vibration bands corresponding to both hydroxyl and carbonyl moieties were present beside that of cyanide group, while in pyridine, the vibration band of the carbonyl group disappeared and only remained that of the hydroxyl group. The higher value and intensity of the wave number of the nitrile band suggested that the enolisation took place at C_2 position.

The relative stereochemistry of the two cyano groups in axial–axial and equatorial–axial isomers was assigned by comparing their electronic effects. On one hand, the cyano group at C_3 position is axial in both isomers (in this position there is no 1,3-diaxial interaction between two methyl groups). Therefore, 3-cyano group has a strong deshielding effect on the axial methyl at C_5. The ^1H NMR spectrum showed two singlets, at δ 1.64 (major isomer) and 1.73 (minor isomer), assigned to axial CH_3 at C_5 position (similar deshielded signal of axial CH_3 was reported for 3 ax-cyano-3,5,5-trimethylcyclohexanone, δ 1.48 CH_3 ax).[37] The H_2 signals at δ 3.50 and 3.55 were assigned respectively to axial–axial and equatorial–axial dicyano isomers by comparison with those of 2-bromocyclohexanone derivatives with the supposition that a cyano group could be assimilated to a bromine atom (2-bromo-4-phenylcyclohexanone: δ 4.38 H_{2eq}/δ 4.87 H_{2ax}, 2-bromo-4-*t*-butylcyclohexanone: δ 4.26 H_{2eq}/δ 4.50 H_{2ax}).[38] On the other hand, the cyano and the carbonyl groups are coplanar in equatorial–axial isomer and their π orbitals are facing each other so that the resulting repulsive effect could promote the stereoisomerisation via an enolisation equilibrium, and leading to the axial–axial dicyano isomer in higher ratio.

In summary, the reaction evolution with nucleophiles $[R_1CHR_2]^-$ was highly dependent upon the sizes of R_1 and R_2. In our investigations, we screened various reaction conditions in the presence of aprotic solvents and in dry media. The best yields were obtained in the absence of solvent. The use of microwave activation either under phase transfer catalysis conditions or on basic solid support (Al_2O_3 or KF/Al_2O_3) avoided solvolysis reactions, and allowed economy in solvent, energy and time. Under these conditions, the reactions were clean and simple, and the yields were very high. The solid support could be recovered at the end of the reactions and the products were easily separated from the support by simple washing.

3. Experimental

3.1. General

The melting points were measured using a Büchi 510 melting point apparatus and were uncorrected. Analytical TLC were obtained using Merck silica gel $^{60}F_{254}$ precoated on aluminum sheets and analytical GC were performed on an FID Carlo Erba, CG 6000 apparatus, fitted with a capillary

column OV1, 15 m. The IR spectra were taken as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily compounds using a Perkin–Elmer 1600 spectrophotometer. The wave numbers ν are expressed in cm^{-1}. The ^1H NMR spectra were recorded at 400, 300, 250 and 200 MHz, respectively by means of Bruker and Gemini 200 BB "Gem 2000" spectrometers and the ^{13}C NMR were recorded in the same spectrometers at 100, 75, 62 and 50 MHz, respectively. Samples were registered in $CDCl_3$ or in DMSO-d_6 solutions using TMS as an internal standard. The chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS. The spectra are reported according to the convention: chemical shift (number of protons, multiplicity, observed coupling constant (Hz) assignement). The multiplicity are reported as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The mass spectra were run on a Delsi/NerMag or on a Varian Mat 311 spectrometer with an ionisating voltage of 70 eV coupled to a gas chromatograph; among the data, only the molecular ion peak and some significative peaks are given with their relative abundance. The microwave apparatus used in this work were a domestic oven Samsung® RE-995 CG operating at a power level of 650 W with temperature evaluation at the end of the reaction by introducing a thermometer inside the sample, and a Synthewave 402 monomode reactor from Prolabo Company (France) with temperature measurement by infrared detection located at the bottom of the sample and temperature control by power modulation from 15 to 300 W. Open vessels were used in both cases. Yields and relative amounts of products were evaluated by gc using an internal standard.

3.1.1. Synthesis of 2,3-epoxyisophorone 1. To an ethanolic solution (20 mL) of isophorone (2.00 g, 14.5 mmol) was added under stirring an aqueous solution of NaOH (0.20 g, 5 mmol in 2 mL H_2O) and 2 mL H_2O_2 35% during 20 min. The temperature was then kept between 30 and 35°C for 1 h. The reaction mixture was cooled down to room temperature, diluted with 15 mL water, and the organic products were extracted from the aqueous layer with 3×20 mL $CHCl_3$. The combined organic layers were washed with water, dried over Na_2SO_4 and evaporated under vacuum at room temperature. The residue was passed through a silica gel column with *n*-hexane/ethyl acetate (9:1) and gave 2,3-epoxyisophorone as a colourless oil (2.20 g, 98%). IR: ν cm^{-1}: 1720, 810, 840, 980, 1010. ^1H NMR 200 MHz ($CDCl_3$): δppm: 0.82 (3H, s, CH_3 at C_5), 0.95 (3H, s, CH_3 at C_5), 1.34 (3H, s, CH_3 at C_3), 1.40–2.70 (4H, m, H_4, H_6), 2.85 (1H, s, H_2), [lit.[39]].

3.1.2. Synthesis of 2,3-dicyano-3,5,5-trimethylcyclohexanone 2. NaCN (0.98 g, 20 mmol, 2 equiv.) was dissolved under stirring in methanol (20 mL). Then 2,3-epoxyisophorone (1.54 g, 10 mmol) was added dropwise to the solution and the reaction mixture was refluxed for 3 h. It was then cooled down to room temperature, concentrated under vacuum then diluted with water (30 mL). The aqueous solution was washed with diethyl ether. The organic layer was dried over Na_2SO_4 and evaporated under vacuum at room temperature. The residue was passed through a silica gel column with *n*-hexane/ethyl acetate (9:1) and gave 2-methoxyisophorone (0.15 g) besides the recovered epoxyisophorone. The aqueous layer was acidified with 10% HCl solution and the organic product was extracted with 20 mL diethyl ether, dried over Na_2SO_4, and the solvent was evaporated. A viscous crude product was obtained which solidified at room temperature. Its recrystallisation from toluene gave white crystals of **2** (1.5 g).

3.2. Epoxyisophorone ring-opening in acetonitrile

3.2.1. General procedure using K_2CO_3/$LiClO_4$/CH_3CN. K_2CO_3 (2.76 g, 20 mmol) was introduced in acetonitrile (10 mL) together with the reagent (15 mmol). Then epoxyisophorone (1.54 g, 10 mmol) and $LiClO_4$ (1.06 g, 10 mmol) were added and the mixture was stirred at room temperature. At the end of the reaction, acetonitrile was removed under vacuum, the crude mixture was diluted with water and the organic products were extracted with either methylene chloride or diethyl ether. The organic layer was dried over Na_2SO_4 and the solvent evaporated to dryness. The residue was chromatographed on a silica gel column with *n*-hexane/ethyl acetate (9:1). The solid compounds were recrystallised from adequat solvent.

3.3. Epoxyisophorone ring-opening under solvent-free conditions

3.3.1. General procedure using K_2CO_3/Aliquat 336. K_2CO_3 (2.76 g, 20 mmol) was intimately blended with the reagent (15 mmol) and Aliquat 336 (200 mg, 0.5 mmol. Epoxyisophorone (1.54 g, 10 mmol) was then added and the mixture was stirred at room temperature and heated in a thermostated oil bath or irradiated under microwaves. At the end of the reaction, the products were isolated by washing with 3×10 mL methylene chloride. The combined extracts were filtered over Florisil to retain mineral salts and remaining aliquat. The solvent was evaporated to dryness. The residue was chromatographed on a silica gel column with *n*-hexane/ethyl acetate. The solid compounds were recrystallised from adequat solvent.

3.3.2. General procedure using KF/Al_2O_3.[40] Neutral alumina (20 g) was stirred for 15 min with an aqueous solution of KF (15 g KF/150 mL H_2O). The mixture was concentrated to dryness under vacuum and kept at 100°C for 30 min. The reagent (15 mmol) was intimately blended with KF/Al_2O_3 (4×reagent mass), epoxyisophorone (1.54 g, 10 mmol) was quickly added to the support and immediately heated in an oil bath or exposed to microwave irradiation. When the reagent was solid, it was dissolved into 5 mL CH_2Cl_2 and mixed with the solid support, and the solvent was evaporated to dryness. At the end of the reaction, the products were eluted from the solid support by washing with 3×10 mL methylene chloride.

3.3.3. 2,3-Dicyano-2,3-dihydroisophorone 2. White crystals, mp 90–92°C from toluene; IR: ν cm^{-1} (KBr): 3545, 3435, 2900–3000, 2220, 2215, 1650,1610; ν (pyridine) 3435, 2900–3000, 2310, 1580. ^1H NMR 300 MHz ($CDCl_3$) δppm: **2** ax–ax: 1.15 (3H, s, CH_{3eq} at C_5), 1.24 (3H, s, CH_3 at C_3), 1.64 (3H, s, CH_{3ax} at C_5), 1.80 (1H, d, J=14.7 Hz, H_{4ax}), 2.22 (1H, dd, J_{AB}=14.6 Hz, $J_{H4eqH6eq}$= 1.8 Hz, H_{4eq}), 2.35 (1H, d, J=12.9 Hz, H_{6ax}), 2.45 (1H, dd, J_{AB}=12.9 Hz, $J_{H6eqH4eq}$=1.8 Hz, H_{6eq}), 3.50 (1H, s, H_2), **2** eq–ax: 1.18 (3H, s, CH_{3eq} at C_5), 1.26 (3H, s, CH_3 at C_3),

1.73 (3H, s, CH_{3ax} at C_5), 1.80 (1H, d, J=14.7 Hz, H_{4ax}), 2.22 (1H, dd, J_{AB}=14.6 Hz, $J_{H4eqH6eq}$=1.8 Hz, H_{4eq}), 2.35 (1H, d, J=12.9 Hz, H_{6ax}), 2.45 (1H, dd, J=12.9 Hz, $J_{H6eqH4eq}$=1.8 Hz, H_{6eq}), 3.55 (1H, s, H_2), **2** enolic form: 1.05 (3H, s, CH_{3eq} at C_5), 1.20 (3H, s, CH_3 at C_3), 1.40 (1H, d, J=14.2 Hz, H_{4ax}), 1.60 (3H, s, CH_{3ax} at C_5), 2.05 (1H, d, J=14.2 Hz, H_{4eq}), 2.15 (2H, s, H_6), 4.30 (1H, s, OH). ^{13}C NMR 75 MHz ($CDCl_3$) δppm: **2** ax–ax: 26.1 (CH_{3eq} at C_5), 28.6 (CH_3 at C_3), 32.6 (CH_{3ax} at C_5), 30.5 (C_5), 36.6 (C_3), 47.6 (C_4), 52 (C_2), 52.5 (C_6), 113.5 (CN_{ax} at C_3), 121 (CN_{ax} at C_2), 196 (C_1), **2** eq–ax: 27.6 (CH_{3eq} at C_5), 30.5 (C_5), 32.0 (CH_3 at C_3), 33.0 (CH_{3ax} at C_5), 36.2 (C_3), 45.2(C_4), 49.7 (C_2), 50.3 (C_6), 105.0 (CN_{ax} at C_3), 120 (CN_{eq} at C_2), 204 (C_1), **2** enolic form: 25.8 (CH_{3eq} at C_5), 28.6 (CH_3 at C_3), 32.3 (CH_{3ax} at C_5), 32.3 (C_5), 39.0 (C_3), 41.6 (C_4), 46.6 (C_6), 83.7 (CN at C_2), 115.5 (CN at C_3), 122.2 (C_2), 169.5 (C_1). MS *m/z* (%), 190 ([M^+], 10), 175 ([M−CH_3], 41), 163 ([M−HCN], 13), 148 ([175−HCN], 22), 56 (100).

3.3.4. Ethyl α-ethoxycarbonyl-2-isophorone acetate 3a. Colourless oil. Anal. calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16; O, 27.00%. Found: C, 64.85; H, 8.19; O, 26.78%. IR: ν cm^{-1}: 2850–3000, 1730, 1665, 1645. ^{1}H NMR 200 MHz ($CDCl_3$): δppm: 1.04 (6H, s, CH_3 at C_5), 1.22 (6H, t, J=7 Hz, $2CH_3$ ethoxy), 1.94 (2H, s, H_4), 2.32 (2H, s, H_6), 4.20 (4H, q, J=7 Hz, $2CH_2$ ethoxy), 4.85 (1H, s, H_α). ^{13}C NMR 50 MHz ($CDCl_3$): δppm: 14.0 (CH_3 ethoxy), 22.4 (CH_3 at C_3), 28.1 ($2CH_3$ at C_5), 32.9 (C_5), 46.8 (C_4), 48.3 (C_6), 50.4 (C_α), 60.5 (CH_2 ethoxy), 129 (C_2), 158.4 (C_3), 168.3 (CO ester), 169 (CO ester), 196 (C_1); MS *m/z* (%) 296 ([M^+], 8), 204 (100), 148 (20), 178 (10).

3.3.5. Ethyl-2-isophorone acetate 3b. Colourless oil. Anal. calcd for $C_{19}H_{20}O_3$: C, 69.61; H, 8.99; O, 21.40%. Found: C, 69.83; H, 9.19; O, 21.23%. IR: ν cm^{-1}: 3600–2700, 1720, 1670, 1630. ^{1}H NMR 200 MHz ($CDCl_3$): δppm: 1.04 (6H, s, gemCH_3 at C_5), 1.25 (3H, t, J=7 Hz, CH_3 ethoxy), 1.94 (3H, s, CH_3 at C_3), 2.30 (4H, s, CH_2 at C_4 and C_6), 3.37 (2H, s, H_α), 4.12 (2H, q, J=7 Hz, CH_2 ethoxy). ^{13}C NMR 50 MHz ($CDCl_3$): δppm: 14.0 (CH_3 ethoxy), 22.5 (CH_3 at C_3), 28.0 ($2CH_3$ at C_5), 32.8 (C_5), 47.4 (C_4), 48.4 (C_6), 50.5 (C_α), 61.5 (CH_2 ethoxy), 128.9 (C_2), 156.6 (C_3), 168.5 (CO ester), 196.9 (C_1). MS *m/z* (%) 224 ([M^+]), 178 (100), 163 (20), 150 (35).

3.3.6. Ethyl α-cyano-2-isophorone acetate 4a. Yellowish oil. Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62; O, 19.25%. Found: C, 67.43; H, 7.82; N, 5.48; O, 19.06%. IR: ν cm^{-1}: 2850–2980, 2230, 1740, 1660, 1600. ^{1}H NMR 200 MHz ($CDCl_3$): δppm: 1.02 (3H, s, CH_3 at C_5), 1.04 (3H, s, CH_3 at C_5), 1.38 (3H, t, J=8.4 Hz, CH_3 ethoxy), 1.41 (3H, s, CH_3 at C_3), 1.83 (2H, AB, J=15 Hz, H_4), 2.53 (2H, AB, J=13.4 Hz, H_6), 4.32 (2H, q, J=8.4 Hz, CH_2 ethoxy), 4.80 (1H, s, H_α). ^{13}C NMR 50 MHz ($CDCl_3$): δppm: 14.4 (CH_3 ethoxy), 21.4 (CH_3 at C_3), 28.4 ($2CH_3$ at C_5), 33.7(C_5), 39.4 (C_4), 47.9 (C_6), 60.5 (C_α), 57 (CH_2 ethoxy), 99.6 (CN), 119.3 (C_2), 149 (C_3), 198 (C_1), MS *m/z* (%) 249 ([M^+], 46), 43 (100).

3.3.7. α-Cyano-2-isophorone acetic acid 4b. Orange crystals, mp 186–188°C from hexane/ethylacetate, 6:4. Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.33%. Found: C, 65.01; H, 6.84; N, 6.28%. IR: ν cm^{-1} 3600–2700, 2250, 1720, 1660, 1600. ^{1}H NMR 200 MHz ($CDCl_3$): δppm: 0.94 (3H, s, CH_3 at C_5), 1.03 (3H, s, CH_3 at C_5), 1.42 (3H, s, CH_3 at C_3), 1.75 (2H, AB, J=15.0 Hz, H_4), 2.30 (2H, AB, J=13.2 Hz, H_6), 3.05 (1H, s, H_α). ^{13}C NMR 50 MHz ($CDCl_3$): δppm: 24.1 (CH_3 at C_3), 27.8 ($2CH_3$ at C_5), 36.0 (C_5), 42.7(C_4), 48.0 (C_6), 61.4 (C_α), 92.0 (CN), 122 (C_2), 138.2 (C_3), 176.0 (CO_2H), 208.2 (C_1).

3.3.8. α-Phenyl-2-isophorone acetonitrile 5. White crystals, mp 90–91°C from petroleum ether. Anal. calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53; O, 6.31%. Found: C, 80.34; H, 7.54; N, 5.39; O, 6.48%. IR: ν cm^{-1} 2980–2850, 2220, 1690, 1610. ^{1}H NMR 200 MHz ($CDCl_3$): δppm: 0.92 (3H, s, CH_3 at C_5), 1.03 (3H, s, CH_3 at C_5), 1.30 (3H, s, CH_3 at C_3), 1.75 (2H, AB, J=15.7 Hz, H_4), 2.48 (2H, AB, J=12.7 Hz, H_6), 3.40 (1H, s, H_α), 7.50 (5H, m, H_{ar}). ^{13}C NMR ($CDCl_3$): δppm: 19.0 (CH_3 at C_3), 28.0 ($2CH_3$ at C_5), 32.9 (C_5), 45.8 (C_4), 51.2 (C_6), 129.8 (C_2), 143.4 (C_3), 193.8 (C_1). MS *m/z* (%), 253([M^+], 46), 238 ([M^+−CH_3], 10), 195 (41), 180 (36), 168 (29), 154 (32), 43 (100).

3.3.9. 4,4,6-Trimethyl-2-oxo-bicyclo[4,1,0] heptane 7,7-dicarbonitrile 6. White crystals, mp 50–51°C from hexane. Anal. calcd for $C_{12}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86%. Found: C, 71.11; H, 6.84; N, 13.92%. IR: ν cm^{-1} 2850–2990, 2230, 1610. ^{1}H NMR 400 MHz ($CDCl_3$): δppm: 0.88 (3H, s, CH_3 at C_5), 1.05 (3H, s, CH_3 at C_5); 1.50 (3H, s, CH_3 at C_3), 1.70 (1H, d, J=16.0 Hz, H_4), 2.00 (1H, d, J=16.0 Hz, H_4), 2.45 (2H, J_{AB}=13.0 Hz, H_6), 3.80 (1H, s, H_2). ^{13}C NMR 100 MHz ($CDCl_3$): δppm: 24.4, 27.0 ($2CH_3$ at C5), 30.6 (CH_3 at C_3), 35.6 (C_5), 41.1 (C_4), 42.5 (C_6), 58.7 (C_2), 66.3 (C_3), 86.5 (C_1''), 110.9 (CN), 111.1 (CN), 178.1 (C_1). MS *m/z* (%), 202 ([M^+], 27), 187 ([M^+−CH_3], 17), 160 (21), 147 (69), 133 (44), 119 (28), 41 (100).

3.3.10. 9-Carbethoxy-2,4,4-trimethyl bicyclo[4,3,0]nona-1,6-dien-8-one 7. White crystals, mp 124–125°C from petroleum ether. Anal. calcd for $C_{15}H_{20}O_3$: C, 72.58; H, 8.06%. Found: C, 72.65; H, 8.12%. ^{1}H NMR 250 MHz ($CDCl_3$): δppm: 0.98 (6H, s, gemCH_3 at C_4), 1.35 (3H, t, J=11.0 Hz, CH_3 ethoxy), 2.20 (2H, s, H_5), 2.55 (2H, d, J_{AB}=12 Hz, H_3), 2.58 (3H, s, CH_3 at C_2), 4.27 (2H, q, J=11 Hz, CH_2 ethoxy), 4.75 (1H, s, H_9), 5.22 (1H, s, H_7). ^{13}C NMR 62 MHz ($CDCl_3$): δppm: 14.0 (CH_3 ethoxy), 28.0 ($2CH_3$ at C_4), 32.2 (C_4), 32.5 (CH_3 at C_2), 36.6 (C_5), 46.0 (C_3), 60.0 (C_9), 67.5 (CH_2 ethoxy), 104.5 (C_7), 133.0 (C_1), 147 (C_6), 151 (C_2), 170.0 (CO ester), 190 (C_8), MS *m/z* (%), 248 ([M^+], 100), 233 ([M^+−CH_3], 10), 219 (40), 203 (19), 187 (18), 159 (14), 43 (24).

3.3.11. α-Cyano-2-isophorone acetamide 8a. White crystals, mp 170–172°C from petroleum ether. Anal. calcd for $C_{12}H_{16}N_2O_2$: C, 65.45; H, 7.27; N, 12.73%. Found: C, 65.51; H, 7.21; N, 12.61%. IR:ν cm^{-1} 3550–3600, 2220, 1640, 1600. ^{1}H NMR 400 MHz, (DMSO-d_6): δppm: 0.95 (3H, s, CH_3 at C_5), 1.04 (3H, s, CH_3 at C_5), 1.29 (3H, s, CH_3), 1.75 (2H, d, J=13.8 Hz, H_4), 2.30 (2H, d, J=13.8 Hz, H_6), 3.05 (1H, s, H_α). ^{13}C NMR 100 MHz, (DMSO-d_6): δppm: 17.8, 25.9 ($2CH_3$ at C_5), 31.9 (CH_3 at C_3), 34.8 (C_5), 40.2 (C_4), 44.2 (C_6), 57.9 (C_α), 93.7 (CN), 122 (C_2), 133.3 (C_3), 165.5 ($CONH_2$), 167.0 (C_1).

3.3.12. 7-Aza-9-cyano-2,4,4-trimethyl bicyclo[4,3,0]-nona-5,9-dien-8-one 8b. White crystals, mp 250–252°C from petroleum ether. Anal. calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.97; N, 13.85; O, 7.91%. Found: C, 71.30; H, 7.06; N, 13.85; O, 7.95%. IR: ν cm^{-1} 3380–3200, 2220, 1630, 1660, 1600. ^1H NMR 400 MHz, (DMSO-d_6): δppm: 1.09 (3H, s, CH_3 at C_4), 1.13 (3H, s, CH_3 at C_4), 1.41 (3H, d, J=7.2 Hz, CH_3 at C_2), 1.44 (1H, dd, J=13.2, 1.0 Hz, H_3), 1.67 (1H, dd, J=13.2, 4.8 Hz, H_3), 3.17 (1H, m, H_2), 5.85 (1H, s, H_5), 10.40 (1H, s, NH). ^{13}C NMR 100 MHz, (DMSO-d_6): δppm: 17.4, 25.6 ($2CH_3$ at C_4), 27.6 (C_2), 30.5 (CH_3 at C_2), 33.2 (C_4), 45.3 (C_3), 100.5 (CN), 113.8 (C_9), 128.2 (C_6), 135 (C_1), 161.4 (C_5), 166 (C_8). MS m/z (%), 202 ([M^+], 27), 187 ([M^+-CH_3], 17), 160 (21), 147 (69), 133 (44), 119 (28), 41 (100).

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