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On the mechanism of the Leuckart reaction. Enantiospecific preparation of (1*R*,2*R*)- and (1*S*,2*S*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)acetamide

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Abstract

The Leuckart reaction of 2-norbornanone and (1*R*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)acetamide *ent*-**1b** furnishes the expected *N*-(2-norbornyl)formamides **11** and *ent*-**10** in good yield. Surprisingly, under the same reaction conditions, the (1*R*)-*N*-(7,7-dimethyl-2-oxo-1-norbornyl)acetamide **1a** gives only **10**, the enantiomeric form of the product obtained from *ent*-**1b**. An explanation of these results is given and a reaction mechanism, based on an unprecedented intramolecular transamidation, is proposed.

1. Introduction

The reductive amination of carbonyl compounds by reaction with formamide **2** and formic acid **4** (Leuckart reaction) is a very useful procedure for the preparation of *N*-formyl derivatives of amines.[1] Nevertheless, the mechanism is still the subject of discussion,[2–5] particularly concerning the reduction step. Thus, Luckasiewicz[2] has suggested the formation of diformylated amino alcohols as intermediates, where reduction should take place via a radical mechanism. However, according to Agwada et al.,[3] the main reaction pathway consists in the previous reduction of the carbonyl group to the corresponding carbinol by hydride transfer from ammonium formate, formed by the hydrolysis of **2**, and subsequent alkylation of formamide.

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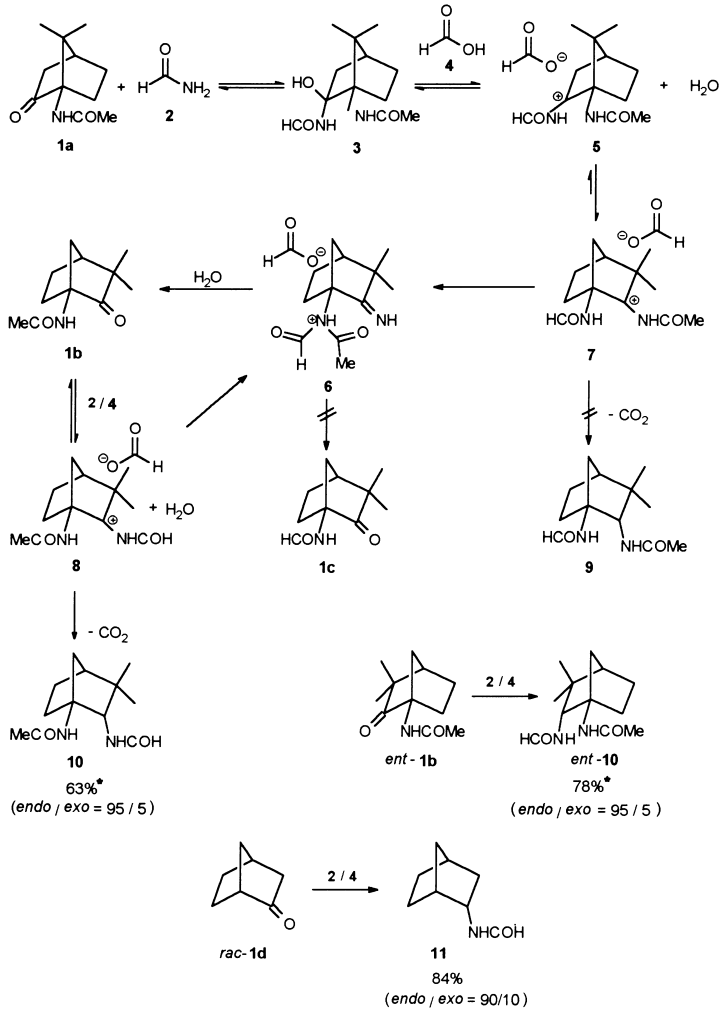
2. Results and discussion

As part of ongoing research work into the enantiospecific synthesis of valuable chiral 1,2-norbornyl derivatives,[6] we have started a study of the Leuckart reaction of different 1-substituted-2-norbornanones **1**. Neither the radical- nor the ketone-reduction mechanisms can account for our results concerning the reaction of these substrates with the **2**/**4** couple. Thus, the formation of the rearranged (1*S*,2*S*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)acetamide **10** (Scheme 1) as the main reaction product of the reductive amination of **1a** precludes any radical mechanism for the reduction step.[7] On the other hand, no alcohols resulting from the reduction of **1a** could be detected, either as reaction products or as transient intermediates, by following the reaction by GC–MS. Consequently, we propose an ionic mechanism for the reductive amination of ketones **1**.[1,2]



* Yields are given in isolated compounds.

Scheme 1. Mechanism of the Leuckart reaction

As shown in Scheme 1, the *endo*-nucleophilic attack[8] of **2** to **1a** affords the *N*-formylated amino alcohol **3**,[1,2] whose protonation followed by ionisation yields cation **5**. Analogous to other 7,7-dimethyl-2-norbornyl cations[8], the nucleophilic attack on **5** is sterically hindered, and a Wagner–Meerwein

rearrangement to cation **7** takes place. This cation is the precursor of ketone **1b** through hydrolysis (the employed acid **4** contains 15% water) of the *N*,*N*-diacylammonium ion **6**, formed from **7** by a transamidation reaction. There is no precedent in the literature for this striking transamidation process. Conversion of 7,7-dimethylketone **1a** into the 3,3-dimethylketone **1b** was demonstrated by following the reaction by GC–MS at different reaction times, and comparison with MS data of the previously synthesised ketone *ent*-**1b**.[6a]

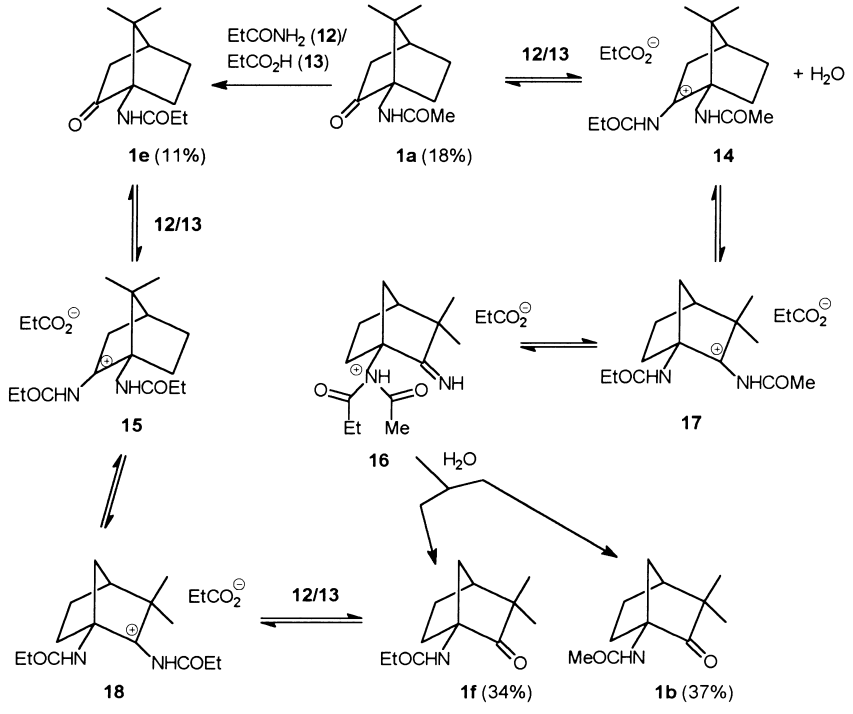
Unlike ketone **1b**, ketone **1c**, which could also be formed by hydrolysis of intermediate **6**, was not detected. This fact can be accounted for by considering the different steric and inductive effects of the H and CH_3 substituents of the carbonyl group. Thus, the $A_{AC}2$ hydrolysis of the formyl group is 10^2–10^3 times faster than that of the acetyl group.[9]

The reaction of the intermediate ketone **1b** with the **2**/**4** couple takes place under the formation of cation **8**, as in the case of **1a**. The slow reduction of this cation (**8**) by the formate counter ion affords **10**, which was the only reaction product isolated after 72 h. It is worth noting that the regioisomer product **9**, which should result by reduction of cation **7**, is 3.5 kcal/mol more stable than **10**, according to calculations with the AM1 method.[10] Thus, the transamidation step is faster than the reduction of cations **7** and **8**, and no equilibration between them takes place under the reaction conditions.

According to the proposed mechanism, the reductive amination of ketone *ent*-**1b**,[6a] under the same reaction conditions as **1a**, affords *ent*-**10**, the enantiomer of the product obtained from **1a**. A predominant *exo*-attack of the formate ion that yields the 2-*endo* epimer is observed, as expected for trapping 2-norbornyl cations.[8] Analogously, the Leuckart reaction of *rac*-2-norbornanone *rac*-**1d** gives a mixture of 2-norbornylformamide epimers **11** (yield=84%) in an *endo/exo* ratio of 9/1 (by ^{1}H NMR, 300 MHz). Similar stereochemical results have been reported in the literature for (1*R*)-fenchone.[11] It is remarkable that the stereochemistry of the final product also precludes a ketone-reduction mechanism in the Leuckart reaction of this kind of compound, because it should mainly lead to the *exo*-derivative.

In order to prove the mechanism proposed by us, especially the intramolecular transamidation process, we have carried out the following experiments, based on the reaction of amide **1a** with different reagents: (1) treatment of **1a** with formic acid, in the absence of formamide. Under these conditions, acid **4** cannot provoke the rearrangement of the ketone, and no reaction is observed at 140–150°C; (2) treatment of **1a** with formamide, in the absence of formic acid. At temperatures below 140–150°C no reaction takes place, but at 150°C the product **10** is slowly formed, following a similar pathway as described in Scheme 1. The reaction is initiated by hydrolysis of **2** with traces of water,[1] which is regenerated during the reaction (steps from **1a** to **8**); and (3) reaction of **1a** with propionamide **12** and propionic acid **13** at 140–150°C. Under the same conditions as with the **2**/**4** couple, this process affords a mixture of (1*S*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)acetamide **1b** (37%), (1*R*)-*N*-(7,7-dimethyl-2-oxo-1-norbornyl)propionamide **1e** (11%), (1*S*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)propionamide **1f** (34%) and the starting material **1a** (18%). The mechanism proposed to explain these results is shown in Scheme 2.

As can be seen in Scheme 2, the combined attack of the **12**/**13** couple to the carbonyl group of **1a** affords cation **14**, which, after rearrangement and transamidation, gives the intermediate **16**. Ketones **1f** and **1b** are then produced by hydrolysis of any of the NH–CO bonds in **16**. In a parallel process, an intermolecular transamidation of **1a** gives the bridgehead propionamide **1e**, which can also produce the ketone **1f** by reaction with the **12**/**13** couple. The main difference with regard to the reaction with formamide and formic acid is the absence of reduction products, demonstrating the essential presence of the formyl hydrogen for the reduction step. The chemical structure of 2-oxo-1-norbornylpropionamides **1e** and **1f** was confirmed by an independent synthesis, through acylation of the already described 7,7- and 3,3-dimethyl-2-oxo-1-norbornylamines[6a] with propionyl chloride and sodium carbonate in CH_2Cl_2.



Scheme 2.

The structure of *ent*-**10** (and subsequently **10**) was determined by X-ray crystal analysis (Fig. 1). The molecules are packed around a fourfold axis joined by equivalent H-bonds. There is an enclosed water solvent molecule, which is not implied in any H-interaction, situated on the axis. The preferred conformation of the formyl group is (*Z*) in the solid state.

Although only a *Z*-conformer is observed in the solid state, the ^{1}H NMR (300 MHz) spectrum of a solution of *ent*-**10** in $CDCl_3$ shows the presence of a small amount of the *E*-isomer. Thus, a ratio of *Z*/*E*=4.9/1 (at room temperature) was determined by means of the different shielding and ^{3}J coupling of the formyl protons (Fig. 2). Under the same conditions, a ratio of *Z*/*E*=3.7/1 is observed for compound **11**.

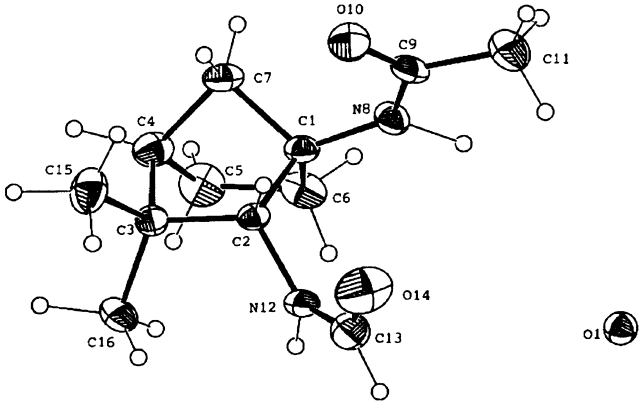


Figure 1. ORTEP diagram of *ent*-**10**

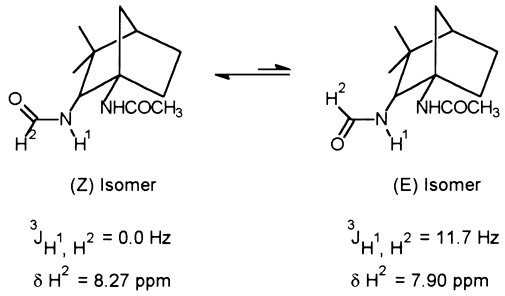


Figure 2. Conformers of the amide *ent*-**10**

In summary, the Leuckart reaction of 2-norbornanones follows a cationic mechanism affording the kinetically favoured product. During the reductive amination of the (1*R*)-*N*-(7,7-dimethyl-2-oxo-1-norbornyl)acetamide **1a** an unprecedented intramolecular transamidation process takes place. Further work in this area, using different bridgehead 2-norbornanones as a starting material, is in progress.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra: Varian-XL 300 and Brucker AC-250 spectrometer, with tetramethylsilane as internal standard. Capillary GC–MS: Shimadzu QP-17A (column type: TRB-1, 30 m) coupled to a Shimadzu QP-5000 mass spectrometer (EI, 60 eV). Melting points: Gallenkamp apparatus; values are uncorrected. Molecular rotations: Perkin–Elmer 241 spectropolarimeter. X-Ray spectroscopy: Philips PW 1100 diffractometer with Cu–K_α radiation (l=1.5418 Å). For the preparation of **1a** and *ent*-**1b** see the literature.[6]

3.2. General procedure for the Leuckart reaction of 2-norbornanones

A mixture of 2.0 mmol of the corresponding 2-norbornanone, **2** (32.2 mmol) and **4** (17.9 mmol) was heated to 150°C. The reaction progress was monitored by GC–MS until total disappearance of starting ketone and intermediate compounds (72 h for **1a**, 24 h for *ent*-**1b** and 12 h for *rac*-**1c**). Lower yields were observed after longer reaction times due to the formation of dark-coloured polymeric products. After completion of the reaction, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with brine (2×10 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by distillation under reduced pressure. The residue was analysed by GC–MS, ^{1}H and ^{13}C NMR, and the *endo*/*exo* ratios were determined by ^{1}H NMR. The crude reaction was purified by crystallisation from hexane (for *rac*-**11**) or MeOH/Et_2O (for **10** and *ent*-**10**). Recrystallisation gave, in all cases, the pure *endo*-epimer.

3.2.1. (1S,2S)-N-(3,3-Dimethyl-2-formylamino-1-norbornyl)acetamide *10*

M.p. 221.8–223.0°C (from MeOH/Et_2O). $[\alpha]_D^{20}$=−62.5 (*c* 0.65, MeOH). For *ent*-**10**, $[\alpha]_D^{20}$=+62.7 (*c* 0.44, MeOH). (*Z*)-**10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (s, 1H), 6.84 (bs, 1H), 6.50 (bs, 1H), 3.81 (ddd, *J*=6.6 Hz, 2.1 Hz, 0.9 Hz, 1H), 2.09 (dd, *J*=9.0 Hz, 2.1 Hz, 1H), 2.05–1.40 (m, 6H), 1.92 (s, 3H), 1.16 (s, 3H), 0.92 (s, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 170.9, 163.2, 66.9, 63.6, 45.8, 38.9, 38.2, 30.7, 25.4, 24.1, 22.8, 20.9; (*E*)-**10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, *J*=11.7 Hz, 1H), 6.17

(bs, 1H), 5.80 (bs, 1H), 4.07 (dd, *J*=10.8 Hz, 2.1 Hz, 1H), 2.61 (dm, *J*=10.5 Hz, 1H), 2.05–1.40 (m, 6H), 1.95 (s, 3H), 1.13 (s, 3H), 0.87 (s, 3H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 170.3, 165.3, 65.7, 60.7, 45.4, 37.9, 37.8, 30.6, 26.0, 24.2, 23.9, 21.6 ppm.

3.2.2. N-*(2*-endo-*Norbornyl)formamide* ***11***

M.p. 64.3–67.4°C (from hexane) (lit.[12] 66°C). (*Z*)-**11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (s, 1H), 5.90 (bs, 1H), 4.20 (m, 1H), 2.50 (bs, 1H), 2.30–2.20 (m, 1H), 2.15–2.00 (m, 1H), 1.70–1.15 (m, 6H), 0.88 (dm, *J*=13.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 49.5, 42.2, 38.1, 37.3, 36.3, 29.6, 21.4; (*E*)-**11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J*=12.0 Hz, 1H), 6.10 (bs, 1H), 3.83 (m, 1H), 2.30–2.20 (m, 2H), 2.15–2.00 (m, 1H), 1.70–1.15 (m, 6H), 0.77 (dm, *J*=12.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 53.2, 42.2, 38.1, 37.6, 36.4, 29.5, 21.1 ppm.

3.3. Synthesis of propionamides ***1e*** *and* ent-***1f***

An amount of 2.2 mmol propionyl chloride was added to a suspension of sodium carbonate (3.0 mmol) and (1*R*)-7,7- or (1*R*)-3,3-dimethyl-2-oxo-1-norbornylamine (2.0 mmol),[6a] respectively, in 15 mL of CH_2Cl_2, at room temperature. After 2 h of reaction the mixture was hydrolysed with water (15 mL), and the organic layer washed with 10% HCl (20 mL), $NaHCO_3$ saturated solution (20 mL) and brine (2×10 mL). After drying with $MgSO_4$ and filtration, the solvent was evaporated under reduced pressure and the crude purified by crystallisation in hexane (*ent*-**1f**) or column chromatography (**1e**; silica gel, hexane/diethylether)

3.3.1. N-*(7,7-Dimethyl-2-oxo-1-norbornyl)propionamide* ***1e***

$[\alpha]_D^{20}$=−13.8 (*c* 0.73, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.88 (bs, 1H), 3.22 (td, *J*=12.7 Hz, 4.0 Hz, 1H), 2.45–1.97 (m, 4H), 2.28 (q, *J*=7.5 Hz, 2H), 1.55–1.22 (m, 2H), 1.25 (s, 3H), 1.15 (t, *J*=7.5 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 214.2, 174.3, 72.9, 48.3, 41.2, 40.4, 30.2, 26.6, 21.9, 21.6, 19.2, 9.8 ppm.

3.3.2. N-*(3,3-Dimethyl-2-oxo-1-norbornyl)propionamide* ent-***1f***

M.p. 64.0–65.5°C (from hexane); $[\alpha]_D^{20}$=−19.1 (*c* 0.95, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): 6.16 (bs, 1H), 2.55 (dd, *J*=10.5 Hz, 2.0 Hz, 1H), 2.25 (q, *J*=7.5 Hz, 2H), 2.16 (m, 1H), 2.00–1.78 (m, 3H), 1.35–1.20 (m, 1H), 1.14 (t, *J*=7.5 Hz, 3H), 1.11 (s, 6H) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 217.9, 173.6, 68.4, 46.1, 43.2, 38.3, 29.8, 26.4, 24.1, 23.5, 21.6, 9.5 ppm.

3.4. Reaction of ***1a*** *with propionamide/propionic acid*

The reaction was carried out using the same conditions as described above for the reaction with formamide and formic acid. After two weeks at 140–150°C, there was no more evolution of the process. At this point, the crude reaction was analysed by GC–MS, showing a mixture of bridgehead amides **1a** (18%), **1b** (37%), **1e** (11%) and **1f** (34%).

Acknowledgements

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