Influence of the Bridgehead Substituent on the Stereoselective Leuckart Reaction of 2-Norbornanones − Skeletal Rearrangement versus Structural Retention

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The synthesis of chiral amine norbornane derivatives has been achieved by means of the Leuckart reaction of various 2-norbornanones. We propose an ionic mechanism for this process in which the formation of a 2-formylamino-2-norbornyl cation is the common initial step. The reaction pathway and the isolated products are strongly dependent on the nature of the bridgehead substituents; hydrogen and alkyl groups yield only enantiopure 2-norbornyl formamides with structural retention, whereas *O*-acyl or *N*-acyl groups favour a pinacol-type skeleton rearrangement through a cascade of Wagner–Meerwein rearrangements and intramolecular transamidations.

The Leuckart reductive amination of carbonyl compounds is a classical procedure for the synthesis of amine precursors.[1,2] This reaction seems to be suitable for the stereoselective synthesis of bicyclic amines, amino alcohols and diamines, with many applications in medicinal chemistry[3] and asymmetric synthesis.[4] Nevertheless, its mechanism still remains unclear and seems to be strongly dependent on the substrate structure.[5−8] In the course of our work on the chemistry of bridgehead norbornane derivatives we have found some unexpected results that have prompted us to propose an ionic mechanism for the reaction of 2-norbornanones with the formamide/formic acid couple.[9] As we have previously reported, the reaction of (1*R*)-*N*-(3,3-dimethyl)- and (1*R*)-*N*-(7,7-dimethyl-1-norbornyl-2-oxo)acetamide yields both the (1*R*,2*R*)- and the (1*S*,2*S*)-enantiomers of *N*-(3,3-dimethyl-2-formylamino-1-norbornyl)acetamide. This fact can only be explained by assuming that the synthetic route involves Wagner−Meerwein rearrangements of 2-norbornyl cations followed by intramolecular transamidations.[9]

However, these results seem to differ from other comparative studies concerning the Leuckart reaction of similar 2-norbornanones.[10] In these studies, carried out at the beginning of the 20th century, the reaction of camphor or fenchone with ammonium formate as a single reagent, or with a mixture of ammonium carbonate/carbamate and formic acid, is reported to take place with structural retention.[10a] This suggests that the substituent linked to the bridgehead position plays a fundamental role in the behaviour of 3,3- and 7,7-dimethyl-2-norbornanones, and can determine the course of the reaction. To gain some insight into the mechanism of the process, in this work we have considered it necessary to establish the stereoelectronic characteristics of the framework substituents that determine whether skeleton rearrangement or structural retention takes place. The substrates selected for this purpose have the same substitution pattern (3,3- or 7,7-dimethyl group), but bear different groups attached to the bridgehead position (H, CH_3, OAc or OCOEt). As the stereochemistry of the final product affords relevant information about the course of the reaction,[9] all the starting ketones were enantiomerically pure.

According to these requirements, (1*S*)-3,3-dimethyl-2-norbornanone (**1**) has been prepared by ozonolysis of (1*S*)-camphene in methanol. (1*R*)-Camphor (**2**) and (1*R*)-fenchone (**3**) are commercially available and have been used without further purification. The synthesis of the acetyl esters **4**[11] and **5**[12] has been accomplished by acetylation (RCOCl/pyr for **4**; Ac_2O/pyr/DMAP for **5**) of (1*R*)-3,3- and (1*R*)-7,7-dimethyl-2-methylene-1-norbornanol, respectively, which were obtained following the procedures described by us in previous papers.[13] The ozonolysis of the 2-methylene esters afforded the desired 1-acyloxy-2-norbornanones **4** and **5** in high yields. (1*R*)-3,3-Dimethyl-2-oxo-1-norbornyl propionate (**6**) has been synthesized by us following the same procedure, with propionyl chloride/pyridine in dichloromethane as the acylation step. For optimal comparison, all the experiments were carried out under the same reaction conditions used previously for bridgehead acetamides: formamide/formic acid (85% in H_2O) at 150 °C.[9] In order to detect any intermediate product formed during the course of the reaction, the Leuckart reaction of all norbornanones was monitored by GC/MS. The obtained results are summarized in Table 1.

In the case of (1*S*)-camphenilone (**1**), (1*R*)-camphor (**2**) and (1*R*)-fenchone (**3**) we only observed simultaneous disappearance of the starting substrate and formation of the

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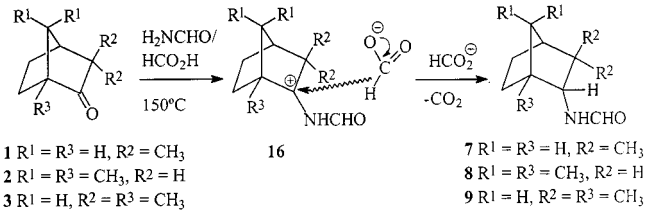
Table 1. Observed results in the Leuckart reaction of 2-norbornanones

Ketone	Product	Yield	*endo*/*exo*[a]	Intermediates[b]
1	**7**	75%	90:10	---
2	**8**	36%	27:73	---
3	**9**	90%	98:2	---
4	**10**	72%	95:5	**12**
5	***ent*-10**	44%	95:5	**13** and ***ent*-12**
6	**11**	70%	95:5	**14** and **15**

[a] Determined by ^{1}H NMR (250 or 300 MHz, $CDCl_3$) of the crude reaction. – [b] Detected by GC/MS; samples were injected directly from the reaction media at different times without pre-treatment.

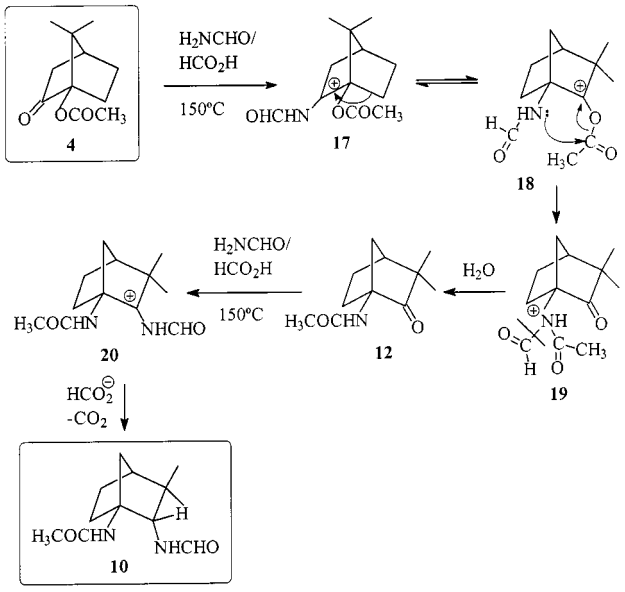
enantiopure *N*-(2-norbornyl)formamides **7**, **8**,[3a,10] and **9**,[10] respectively (see Scheme 1). A bridgehead methyl group or a hydrogen atom are thus not able to favour any skeletal rearrangement, and fenchone and camphor provide different products with structural retention. Consequently, we propose an ionic mechanism that involves an intermediate carbocation **16**, formed by reaction of the carbonyl group with formamide in acid medium. Unlike the 2-(trifluoromethanesulfonyloxy)-2-norbornylcarbenium ions studied by us in the reaction of 1-methyl-2-norbornanones with Tf_2O, no Wagner–Meerwein rearrangement takes place because of the stabilisation exerted by the formylamine group.[14] However, as noted by a referee, we cannot discard the addition of ammonia instead of formamide, on the basis of the equilibrium between formamide/formic acid mixture and ammonium formate at 150 °C in the presence of water. Nevertheless, this would lead to the formation of 2-norbornylamines that were not detected by us while monitoring the progress of the reaction.[15] The *endo*/*exo* ratios of the isolated formamides are in agreement with the steric hindrance shown by these 2-norbornyl cations towards the nucleophilic attack of the formate ion (Scheme 1).[16,17]



Scheme 1

The reaction of (1*R*)-7,7-dimethyl-2-oxo-1-norbornyl acetate (**4**) was carried out under the same conditions as for **2**. The substitution of the bridgehead methyl group by an electron-releasing substituent like acetoxy causes a very different behaviour. As shown in Table 1, the monitoring of the reaction by GC/MS reveals the formation of (1*S*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)acetamide (**12**) as an intermediate in the process, followed by the appearance of (1*S*,2*S*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)acetamide (**10**) as the only final product. The absolute configuration of diamide **10** {$[\alpha]_D^{20}$ = +62.9 (*c* = 0.95, MeOH)} is the same as that of the product described by us using (1*R*)-*N*-(7,7-dimethyl-2-oxo-1-norbornyl)acetamide (***ent*-13**) as substrate {$[\alpha]_D^{20}$ = +62.7 (*c* = 0.44, MeOH)}.[9]

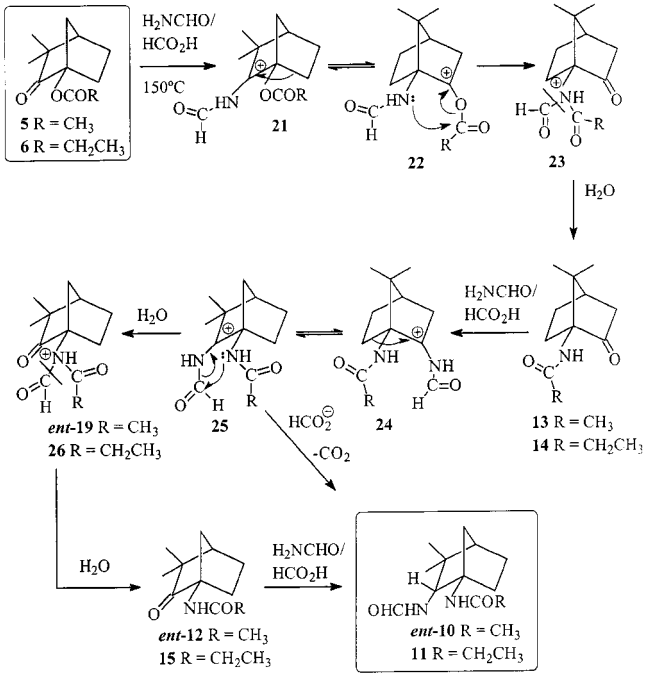
The mechanism proposed to explain these striking results is exposed in Scheme 2. The first step is the formation of carbocation **17**, followed by a Wagner–Meerwein rearrangement. According to the substitution pattern, this transposition could be compared with a pinacol-type rearrangement involving the norbornane skeleton. As no norbornyl esters were detected by GC/MS in the reaction medium, we can conclude that the reduction of cations **17** and **18** is slower than the intramolecular transacylation that provides the protonated imide **19** from **18**. Considering the different steric and inductive effects of the H and CH_3 substituents of the carbonyl group,[18] the selective hydrolysis of the N–COH bond in this intermediate explains the detection of (1*S*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)acetamide (**12**) by GC/MS in the course of the reaction. As previously described,[9] amide **12** reacts by formation of cation **20**, followed by formate anion attack at the *exo*-face, to give the diamide **10**.



Scheme 2

At this point, we could postulate that the driving force for the skeletal rearrangement is the electron-releasing substituent at the bridgehead position because of the stabilisation exerted over the resulting carbocation. The simultaneous presence of a 7,7-dimethyl moiety that hinders the reduction of the intermediate cation **17** seems indirectly to favour the rearrangement. According to this, we could expect that the Leuckart reaction of esters **5** and **6** (containing 3,3-dimethyl groups that do not hinder the reduction by the formate ion) would take place with structural retention, thus providing the corresponding β-amino alcohol precursors. Nevertheless, the reaction of acetate **5** with the formamide/formic acid couple implies a very different pathway

than that followed by (1*R*)-fenchone (**3**) and (1*R*)-*N*-(3,3-dimethyl-1-norbornyl-2-oxo)acetamide (***ent*-12**)[9] (see Table 1). In this case, the final product is not the expected β-amide ester but the enantiomer of **10**, (1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)acetamide (***ent*-10**) {$[\alpha]_D^{20} = -64.1$ ($c = 0.94$, MeOH)}. As two acetamide intermediates **13** and ***ent*-12** are detected by GC/MS, more than one skeletal rearrangement must take place in the Leuckart reaction of this ketone (see Scheme 3). Substitution of the OCOMe group by OCOEt leads to similar results, and two intermediate propionamides **14** and **15**[9] are detected during the reaction of **6** by GC/MS-monitoring (see Table 1). The only isolated final product is (1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)propionamide (**11**) in good yield {$[\alpha]_D^{20} = -61.3$ ($c = 0.96$, MeOH)}.



Scheme 3

The proposed reaction mechanism is shown in Scheme 3. According to this scheme, ketones **5** and **6** react with formamide and formic acid to give cation **21**. Unlike similar cations **16** (see Scheme 1) or **20** (see Scheme 2) that have the 3,3-dimethyl moiety, the reduction step is not favoured for **21** and the presence of the acyloxy group in the bridgehead position provokes the skeletal rearrangement. In spite of the higher stabilization that the nitrogen atom can exert in **21**, the key step that shifts the equilibrium between **21** and **22** to the right seems to be the intramolecular transacylation that provides imide **23** (Scheme 3). After selective cleavage of the N−COH bond, the (1*S*)-*N*-(7,7-dimethyl-1-norbornyl-2-oxo)amides **13** or **14** are formed in the reaction media as the first intermediates detected by GC/MS. Again, we can postulate the formation of a 7,7-dimethyl carbocation **24**, which undergoes a second Wagner−Meerwein rearrangement to provide cation **25**. There are two possible reaction pathways that give rise to the final products: one is the direct reduction to give the diamides ***ent*-10** and **11**, and the other one involves a new intramolecular transamidation to give the imides ***ent*-19** and **26**. After detection by GC/MS of the 7,7-dimethylamides **13** and **14**, we have observed in the reaction media the simultaneous formation of the diamides ***ent*-10** and **11**, as well as the intermediates (1*R*)-*N*-(3,3-dimethyl-1-norbornyl-2-oxo)amides ***ent*-12** and **15**. Therefore, both reaction pathways must be competitive, and yield finally the (1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)amides ***ent*-10** and **11** from esters **5** and **6**, respectively.

In summary, it can be concluded that the Leuckart reaction of 2-norbornanones has a common initial step that implies the formation of a differently substituted 2-formylamine-2-norbornyl carbocation. The subsequent evolution of this cation is determined by the nature of the groups attached to the framework. In all cases, bridgehead hydrogen and alkyl groups favour the reduction step, and yield exclusively *N*-(2-norbornyl)formamides with structural retention. However, the presence of *N*-acyl or *O*-acyl groups at C1 can provoke a pinacol-type rearrangement, followed by an intramolecular transamidation involving the norbornane framework, which competes with the reduction by the formate ion. As the presence of the 7,7-dimethyl groups hinders the reduction step, the position of the *gem*-dimethyl moiety in the 2-norbornanones also plays an important role in the reaction pathway.

Both reaction pathways are highly stereoselective, and all the isolated compounds are enantiomerically pure. Consequently, this reaction constitutes a useful tool in the synthesis of chiral amine derivatives with potential applications as anticancer agent precursors or chiral ligands in asymmetric synthesis.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra: Varian-XL 300 and Bruker 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. For the synthesis of the 2-oxo-1-norbornyl esters **4** and **5**, see refs.[11−13] The propionyl ester **6** was prepared by the same procedure as **4**. The propionamides **14** and **15** were obtained by independent syntheses.[9]

General Procedure for the Leuckart Reaction of 2-Norbornanones: A mixture of 2.0 mmol of the corresponding 2-norbornanone, formamide (32.2 mmol) and formic acid (17.9 mmol) was heated to 150 °C. The reaction progress was monitored by GC/MS until total disappearance of the starting ketone and the intermediate compounds (3−72 h); the samples were injected directly from the reaction media at different times without pre-treatment. Lower yields were observed after long reaction times due to the formation of dark-coloured polymeric products. After completion of the reaction, a saturated aqueous solution of $NaHCO_3$ (30 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 30 mL). The organic layer was washed with brine (30 mL) and dried over anhyd-

rous $MgSO_4$. After filtration, the solvent was removed by distillation under reduced pressure. The residue was analysed by ^1H NMR spectroscopy to determine the *endo*/*exo* ratios. The crude reaction was purified by crystallisation from hexane (for **7** and **9)** or MeOH/Et_2O (for **10**, **11** and *ent*-**10**). Recrystallisation gave the pure 2-*endo* epimer in all cases. Compound **8** was purified by column chromatography [silica gel, hexane/ethyl acetate (3:1)], followed by recrystallisation from hexane, to isolate the pure 2-*exo* isomer. The enantiopure formamides were characterised by MS (EI), ^1H and ^{13}C NMR and IR spectroscopy, melting point, elemental analysis and optical rotation, and the values agree with those previously reported for **8** and **9**.[3a,10] The ^1H NMR spectra of all formamides in $CDCl_3$ shows the presence of the two (*E*) and (*Z*)-isomers, whose relative ratios at room temperature were determined by means of the different shielding and ^3J couplings of the formyl protons.[9]

(1*S*,2*S*)-*N*-(3,3-dimethyl-2-norbornyl)formamide (7): 75% yield from ketone **1**. *Z*/*E* ($CDCl_3$) = 4.8:1. − ^1H NMR (250 MHz, $CDCl_3$) δ = 8.23 (s, 1 H, *Z*), 8.02 (d, *J* = 11.7 Hz, 1 H, *E*), 6.15 (br. s, 1 H, *E*), 5.81 (br. s, 1 H, *Z*), 3.88 (dd, *J* = 8.8, 4.1 Hz, 1 H, *Z*), 3.31 (dd, *J* = 10.3, 3.9 Hz, 1 H, *E*), 2.33 (br. s, 1 H, *Z*), 2.25 (br. s, 1 H, *E*), 1.85 (br. s, 1 H), 1.80−1.55 (m, 2 H), 1.50−1.15 (m, 4 H), 1.09 (s, 3 H, *Z*), 1.03 (s, 3 H, *E*), 0.83 (s, 3 H). − $[\alpha]_D^{20}$ = −24.5 (*c* = 0.92, MeOH).

(1*R*,2*R*)-*N*-(1,7,7-trimethyl-2-norbornyl)formamide (8):[10] 36% yield from ketone **3**. *Z*/*E* ($CDCl_3$) = 2.2:1. − ^1H NMR (250 MHz, $CDCl_3$) δ = 8.15 (s, 1 H, *Z*), 7.97 (d, *J* = 11.7 Hz, 1 H, *E*), 6.40 (br. s, 1 H, *E*), 5.90 (br. s, 1 H, *Z*), 3.97 (td, *J* = 9.2, 5.0 Hz, 1 H, *Z*), 3.31 (td, *J* = 10.0, 5.0 Hz, 1 H, *E*), 1.90−1.10 (m, 7 H), 0.91 (s, 3 H, *Z*), 0.88 (s, 3 H, *E*), 0.87 (s, 3 H, *E*), 0.86 (s, 3 H, *Z*), 0.85 (s, 3 H, *E*), 0.84 (s, 3 H, *Z*). − $[\alpha]_D^{20}$ = +18.7 (*c* = 0.62, MeOH).

(1*R*,2*S*)-*N*-(1,3,3-trimethyl-2-norbornyl)formamide (9):[3a] 90% yield from ketone **2**. *Z*/*E* ($CDCl_3$) =1.7:1. − ^1H NMR (250 MHz, $CDCl_3$) δ = 8.31 (s, 1 H, *Z*), 7.90 (d, *J* = 11.6 Hz, 1 H, *E*), 6.30 (br. s, 1 H, *E*), 5.79 (br. s, 1 H, *Z*), 3.72 (d, *J* = 9.8 Hz, 1 H, *Z*), 2.90 (dd, *J* = 10.9, 1.8 Hz, 1 H, *E*), 1.80 (m, 1 H), 1.75−1.40 (m, 3 H), 1.30−1.15 (m, 3 H), 1.11 (s, 3 H, *Z*), 1.06 (s, 3 H, *Z*), 1.06 (s, 3 H, *E*), 1.04 (s, 3 H, *E*), 0.84 (s, 3 H, *E*), 0.81 (s, 3 H, *Z*). − $[\alpha]_D^{20}$ = +49.6 (*c* = 0.92, MeOH).

(1*S*,2*S*)-*N*-(3,3-dimethyl-2-formylamine-1-norbornyl)acetamide (10): 61% yield from ester **4**. − $[\alpha]_D^{20}$ = +62.9 (*c* = 0.95, MeOH). For spectroscopic data, see ref.[9]

(1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamine-1-norbornyl)acetamide (*ent*-10): 44% yield from ester **5**. − $[\alpha]_D^{20}$ = −64.1 (*c* = 0.94, MeOH). For spectroscopic data, see ref.[9]

(1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamine-1-norbornyl)propionamide (11): 70% yield from ester **6**. *Z*/*E* ($CDCl_3$) = 4.7:1. − ^1H NMR (300 MHz, $CDCl_3$) δ = 8.28 (s, 1 H, *Z*), 7.88 (d, *J* = 11.4 Hz, 1 H, *E*), 6.81 (br. s, 1 H, *Z*), 6.59 (br. s, 1 H, *Z*), 6.43 (br. s, 1 H, *E*), 5.76 (br. s, 1 H, *E*), 4.09 (dm, *J* = 11.1 Hz, 1 H, *E*), 3.82 (dm, *J* = 6.7 Hz, 1 H, *Z*), 2.65 (dm, *J* = 10.2 Hz, 1 H, *E*), 2.16 (q, *J* = 3.5 Hz, 2 H, *E*), 2.14 (q, *J* = 7.5 Hz, 2 H, *Z*), 2.07 (dd, *J* = 9.7, 1.1 Hz, 1 H, *Z*), 2.05−1.55 (m, 6 H), 1.16 (s, 3 H, *Z*), 1.11 (s, 3 H, *E*), 1.10 (t, *J* = 7.5 Hz, 3 H, *E*), 1.09 (t, *J* = 7.5 Hz, 3 H, *Z*), 0.92 (s, 3 H, *Z*), 0.87 (s, 3 H, *E*). − $[\alpha]_D^{20}$ = −61.33 (*c* = 0.96, MeOH).

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