1,3,4,5-Tetrahydroazepin-2-ones by Dearomatising Anionic Cyclisation of *N*-Allyl-1-Naphthamides

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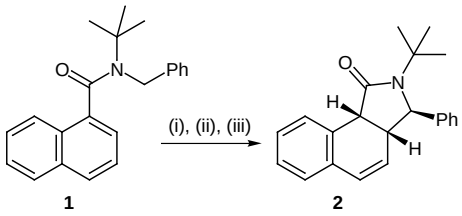
Abstract: On treatment with *t*-BuLi and DMPU, 1-naphthamides bearing *N*-allyl or *N*-prenyl substituents cyclise to give a mixture of products from which seven-membered lactams can be isolated in up to 73% yield – the first example of an organolithium–C=C cyclisation leading to a seven-membered ring.

Key words: amide, cyclization, lithium, azepin, dearomatisation

We recently described a cyclisation reaction of *N*-benzyl naphthamides[1] **1** and *N*-benzyl benzamides[2] which is triggered by deprotonation with strong base (*t*-BuLi) in the presence of an additive such as HMPA or DMPU, and which leads to loss of aromaticity in one ring (Scheme 1). The products of the cyclisation **2** contain a substituted pyrrolidinone ring, formed with high stereoselectivity, but invariably bearing a phenyl group in the 2-position. In an attempt to broaden the scope of this new reaction, we surveyed some other nitrogen substituents with moderate anion stabilising ability,[3] and found that allylic *N*-substituents also allowed the cyclisation to take place.

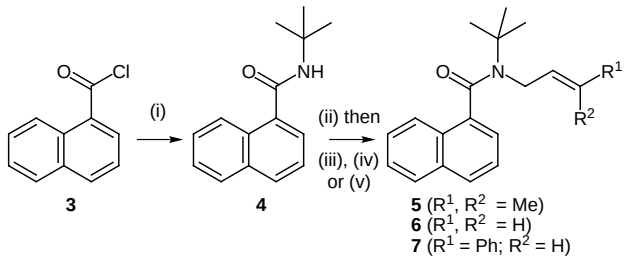


1 **2**

A dearomatising anionic cyclisation; (i) t-BuLi, –78 °C, THF, 2 h; (ii) DMPU or HMPA (6 equiv.), –78 °C, 16 h; (iii) NH_4Cl (82%)

Scheme 1

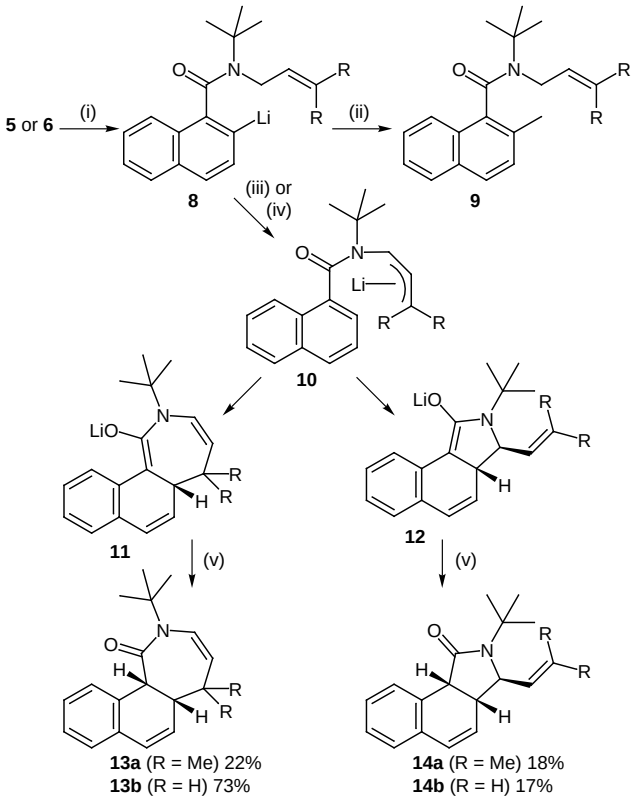
We made *N*-*t*-butyl-*N*-prenyl-1-naphthamide **5** by *N*-alkylation of *N*-*t*-butyl-1-naphthamide **4** (Scheme 2). The amide was treated with *t*-BuLi at –78 °C for 2 h and the resulting organolithium **8** quenched with MeI. Only the 2-methyl product **9** was formed, suggesting that the organolithium is principally an ortholithiated and not an α-lithiated species. Prenyl must be a less powerful anion-stabiliser than phenyl, since lithiated *N*-benzyl naphthamides react with MeI to give only the α-methylated product.[1,4]



3 **4** **5** (R^1, R^2 = Me) **6** (R^1, R^2 = H) **7** (R^1 = Ph; R^2 = H)

Synthesis of the starting materials; (i) t-$BuNH_2$, NaOH, CH_2Cl_2 (98%); (ii) NaH, DMF; (iii) prenyl bromide (46%); (iv) allyl bromide (94%); (v) cinnamyl bromide (68%)

Scheme 2

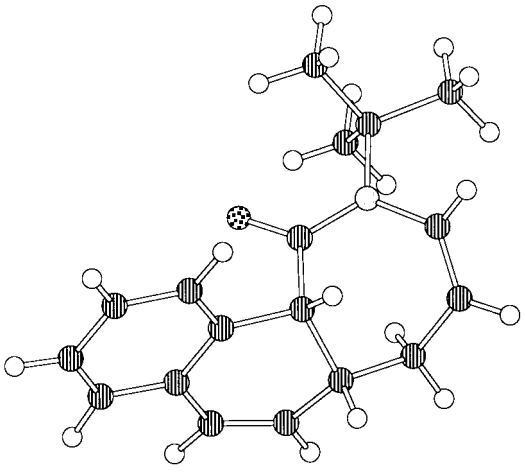


Cyclisation of *N*-allyl-1-naphthamides; (i) *t*-BuLi, THF, –78 °C, 2 h; (ii) MeI (91%, $R^1 = R^2 = Me$); (iii) DMPU (6 equiv.), –50 °C, 16 h; (iv) HMPA (6 equiv.), –78 °C, 16 h; (v) NH_4Cl

Scheme 3

In the *N*-benzyl series, we had found that DMPU or HMPA promotes the cyclisation by favouring an anion translocation from the *ortho* to the α position.[4] In the presence of DMPU at –50 °C for 16 h, the ortholithiated *N*-prenyl amide **8** must also undergo anion translocation to **10**, because protonation returned a moderate yield of dearomatised cyclised products **13a** and **14a**, presumably via the enolates **11** and **12**. Remarkably, the major product **13** is a tetrahydroazepinone formed by attack at the γ position of the lithiated prenyl group.[5,6] Seven-membered rings are typically slow to form by cyclisation reactions, and to our knowledge had never been made previously by an organolithium cyclisation onto a C=C double bond.[7] In this case, the probable *Z*-geometry[6] of the intermediate **10** will favour 7-ring formation.

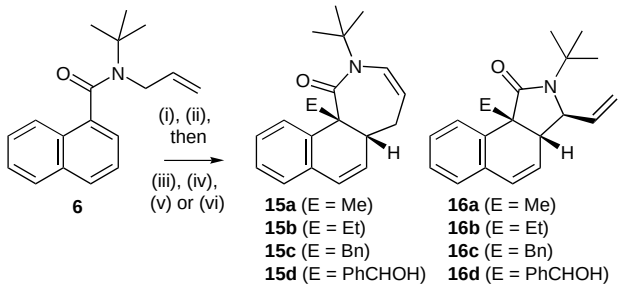
In view of the structural similarity between these rare[8] cyclic *N*-acyl enamines and the pharmaceutically important benzazepin-2-ones,[9,10] we aimed to optimise the formation of the seven- over the five-membered ring product. Removing the geminal methyl groups of the prenyl substituent improved the yield of the reaction and increased the selectivity for seven-membered ring formation. Allylation of *N*-*t*-butyl-1-naphthamide gave the starting material **6**, which was lithiated with *t*-BuLi and cyclised in the presence of DMPU or HMPA at –50 °C or at –78 °C. Protonation gave the seven-membered ring product **13b** in 73% isolated yield,[11] along with only 17% of the five-membered ring product **14b**. The structure and stereochemistry of the product was confirmed by an X-ray crystal structure, shown in the Figure.



X-ray crystal structure of **13b**

Figure

The initial products of the cyclisation, lactam enolates **11** and **12**, could be alkylated to give more highly substituted seven-membered ring products, as shown in Scheme 4 and the Table. Five-membered rings were still among the by-products of the reaction, but single diastereoisomers were formed in each case, even with benzaldehyde, which gave a single aldol product **15d** of unknown stereochemistry at the hydroxyl-bearing centre.



6

15a (E = Me)
15b (E = Et)
15c (E = Bn)
15d (E = PhCHOH)

16a (E = Me)
16b (E = Et)
16c (E = Bn)
16d (E = PhCHOH)

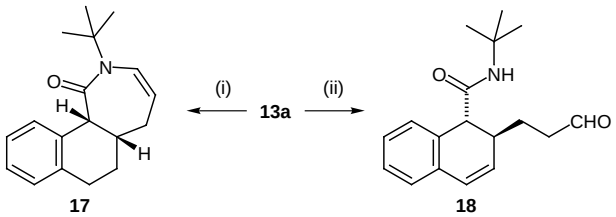
Cyclisation–alkylation of **6**; (i) *t*-BuLi, THF, –78 °C, 2 h; (ii) DMPU (6 equiv.), –50 °C, 16 h; (iii) MeI; (iv) EtI; (v) BnBr; (vi) PhCHO

Scheme 4

entry	electrophile	**15**, yield (%)	**16**, yield (%)
1	MeI	**15a**, 56	**16a**, 25
2	EtI	**15b**, 66	**16b**, 27
3	BnBr	**15c**, 68	**16c**, 23
4	PhCHO	**15d**, 48	**16d**, 9

The C=C double bonds of **13b** could be reacted selectively under hydrogenation or hydrolysis conditions. Hydrogen over palladium on carbon reduced the styrene double bond of **13b** to give a quantitative yield of **17**. Hydrolysis of **13b**'s *N*-acyl enamine group with aqueous HCl in THF gave the aldehyde **18** in 76% yield (Scheme 5), in which the *trans* stereochemistry presumably arises by epimerisation of a first-formed *cis* isomer.[12] The cyclisation/hydrolysis sequence represents in this case a formal addition of the homoenolate of propionaldehyde[13] to the naphthalene ring.

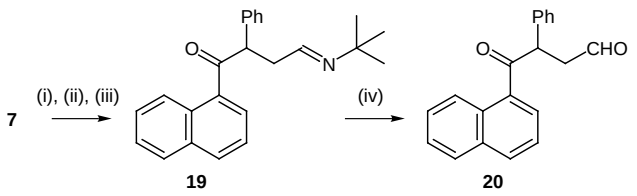
In a final attempt to increase still further the selectivity of the reaction for seven-membered ring formation we tried cyclising the *N*-cinnamyl compound **7**. This time, after treatment with *t*-BuLi and DMPU (–50 °C, 16 h) no cyclisation product was observed: instead, we obtained a quantitative yield of the unstable imine **19**, which hydrolysed during purification to give the aldehyde **20** in 46% yield. The imine is formed by an N→C acyl transfer:[14] the organolithium attacks the amide carbonyl group instead of the aromatic ring.



17 **18**

Transformations of the seven-membered lactam;(i) H_2 (1 atm.), Pd/C, 16 h (quant.); (ii) HCl, H_2O, THF (76%)

Scheme 5



Attempted cyclisation of N-cinnamyl-1-naphthamide **7**; (i) *t*-BuLi, THF, –78 °C, 2 h; (ii) DMPU (6 equiv.), –50 °C, 16 h; (iii) NH_4Cl (quant.); (iv) SiO_2 chromatography (46%)

Scheme 6

Acknowledgement

We are grateful to the EPSRC for a CASE award (to AA).

References and Notes

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(10) Kasparek, S. in *Adv. Heterocyclic Chem.;* Katritzky, A. R.; Boulton, A. J. Eds.; Academic Press: New York, 1974; Vol. 17; p. 45.
(11) *t*-BuLi (2.60ml of a 1.5M solution in pentane, 1.3 equiv.) was added dropwise to a stirred solution of **6** (0.802 g, 3.0 mmol) in THF (50 ml) under nitrogen at –78°C. After 2hrs DMPU (2.18mL, 6 equiv.) was added and the reaction mixture was warmed to -50°C and stirred at this temperature overnight. Saturated ammonium chloride solution was then added and the mixture was allowed to warm to room temperature. Water (100ml) was added and the organic phase was extracted with ether (3 x 100ml), washed with water (3 x 100ml) and brine (2 x 100ml), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography [7:1 petrolum ether (b.p. 40-60 °C)–ethyl acetate] gave the 1,3,4,5-tetrahydroazepin-2-one **13b** (0.582g, 73%) as a white solid, m.p. 131-132 °C; ν_{max} (CH_2Cl_2)/cm^{-1} 3054, 3019, 2973, 2855, 1662 and 1399; δ_H (300 MHz; $CDCl_3$) 7.16-6.82 (4H, m), 6.36 (1H, dd, *J*=9.5 and 2.5), 6.16 (1H, dd, *J*=7.5 and 1.5), 5.77 (1H, q, *J*=7.5), 5.54 (1H, dd, *J*=9.5 and 2.5), 3.92 (1H, d, *J*=9.5), 3.26 (1H, q×m, *J*=9.5), 2.18 (2H, m, CH_2) and 1.33 (9H, s, *t*-Bu); δ_C ($CDCl_3$) 173.9, 134.6, 133.5, 130.8, 129.6, 128.2, 127.6, 127.5, 127.4, 126.3, 121.2, 58.2, 48.1, 45.0, 28.4 and 28.3 (CH_2); m/z CI 268 (100%, $M+H^+$) EI 267 (20%, M), 128 (75%) and 57 (100%, *t*-Bu). (Found M^+267.1623. $C_{18}H_{21}NO$ requires *M* 267.1623).
(12) The *trans* stereochemistry of **18** was confirmed by a strong NOE between C*H*CONH*t*-Bu and CH_2CHO. We assume that **15a-d** have a *cis* ring junction by analogy with **13b**.
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