Pyrrolidinone-fused Cyclohexenones by Regioselective Dearomatising Anionic Cyclisation of 2-, 3- or 4-Methoxybenzamides

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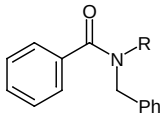
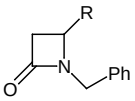
Abstract: On treatment with *t*-BuLi in the presence of HMPA, 2-, 3- or 4-methoxybenzamides (*o*-, *m*- or *p*-anisamides) bearing *N*-benzyl substituents cyclise with dearomatisation to give methyl dienyl ethers which hydrolyse to give single stereo- and regioisomers of pyrrolidine-fused cyclohexenones. The bicyclic enones are versatile synthetic intermediates which undergo transformations such as stereoselective reduction and conjugate addition, regioselective Baeyer-Villiger oxidation, bromination and hydrogenation.

Key words: amide, cyclisation, lithiation, enone, regioselectivity

The lithiation α to nitrogen of aromatic amides bearing benzylic substituents has been known for many years, with Fraser[1] and Durst[2] reporting the α-lithiation by LDA of *N*-benzylamides **1a**, **2** and **3**. In 1999, we reported[3] that the organolithiums derived from simple *N*-benzyl benzamides **1a** and **1b** are unstable at −78 °C in the presence of HMPA: they undergo a cyclisation reaction with loss of aromaticity in the benzamide ring, leading to pyrrolidine-fused cyclohexadienes **5** and **6** (Scheme 1). The intermediate in the cyclisation reactions is an extended enolate **4**, which unfortunately does not react regioselectively with electrophiles - a serious limitation to the synthetic application of the dearomatising reaction.



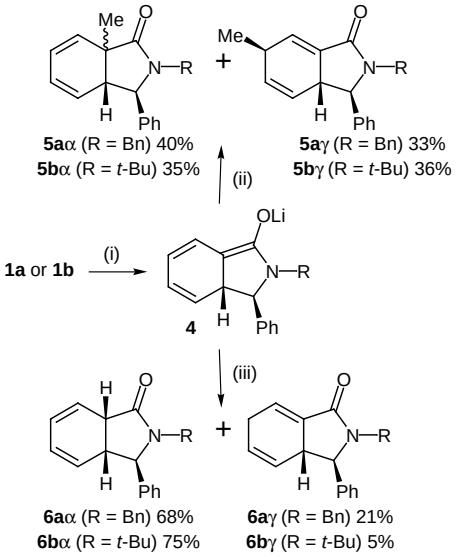
1a, R = Bn
1b, R = *t*-Bu



2, R = Ph
3, R = allyl

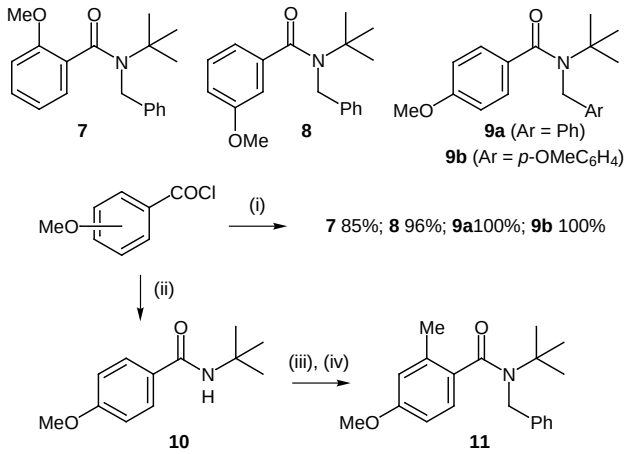
In this Letter, we now report that benzamides **7**-**9** and **11** bearing methoxy groups also cyclise with dearomatisation, but that the regioselectivity of the electrophilic quench step is immaterial to the formation of single final product because hydrolysis of a mixture of first-formed dienyl ethers usually generates a single regioisomer of a cyclohexenone. The cyclohexenone products are versatile synthetic intermediates which undergo stereoselective functionalisation.[4]

The four anisamides (methoxybenzamides) **7**, **8**, **9a** and **9b** were made by acylation of *N*-benzyl-*t*-butyl amine or *N*-*p*-methoxybenzyl-*t*-butyl amine. Amide **11** was made by ortholithiation[5] and benzylation of the secondary benzamide **10** (Scheme 2). They were each treated under our standard conditions[3] for dearomatising cyclisation (Method A: *t*-BuLi, THF, HMPA, −78 °C, or, for **8** and **11**, −40 °C) and the reactions were quenched with aqueous ammonium chloride (Scheme 3).



Scheme 1 Lithiation and Dearomatisation of *N*-Benzyl Amides; (i) *t*-BuLi, THF, HMPA, −78 °C; (ii) MeI; (iii) NH_4Cl, H_2O

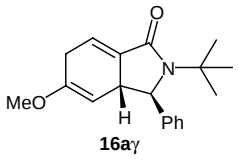
The *o*-anisamide **7** was the only amide to cyclise with a lack of stereoselectivity, giving 76% of the cyclised product **12** as a mixture of stereoisomers,[6] which were separable by flash chromatography on silica, though slightly unstable. Each of *exo*- and *endo*-**12** was obtained as a single regioisomer only. The *m*-anisamide **8**, which in principle could cyclise onto either the 2- or the 6-position of the ring, similarly gave only a single regioisomer **14**, but the cyclisation required temperatures of −40 °C to return good yields of **14**. The *p*-anisamides **9a**, **9b** and **11** cyclised stereoselectively, but sometimes gave mixtures of regioisomers arising from α- or γ-attack on the enolate intermediate. **16a** and **16b** were typically obtained as single regioisomers;[7] **19**α and **19**γ were obtained in a 5:1 ratio; and **18**α and **18**γ (produced by alkylating the intermediate enolate with MeI) were obtained in a 1:2 ratio.



Scheme 2 Anisamides as starting materials. (i) BnNH*t*-Bu for **9a** or *p*-$MeOC_6H_4CH_2NHt$-Bu (made quantitatively from *t*-$BuNH_2$ and *p*-methoxybenzyl chloride) for **9b**, NaOH, H_2O, CH_2Cl_2, 24 h: 85% **7**, 96% **8**, 100%, **9a**; 100%, **9b**; (ii) *t*-$BuNH_2$, CH_2Cl_2, NaOH, H_2O: 100%; (iii) 1. *n*-BuLi, THF, 0 °C, 30 min; 2. *t*-BuLi, −78 °C, 1 h; 3. MeI: 63%; (iv) 1. NaH, DMF, 2. BnBr: 72%.

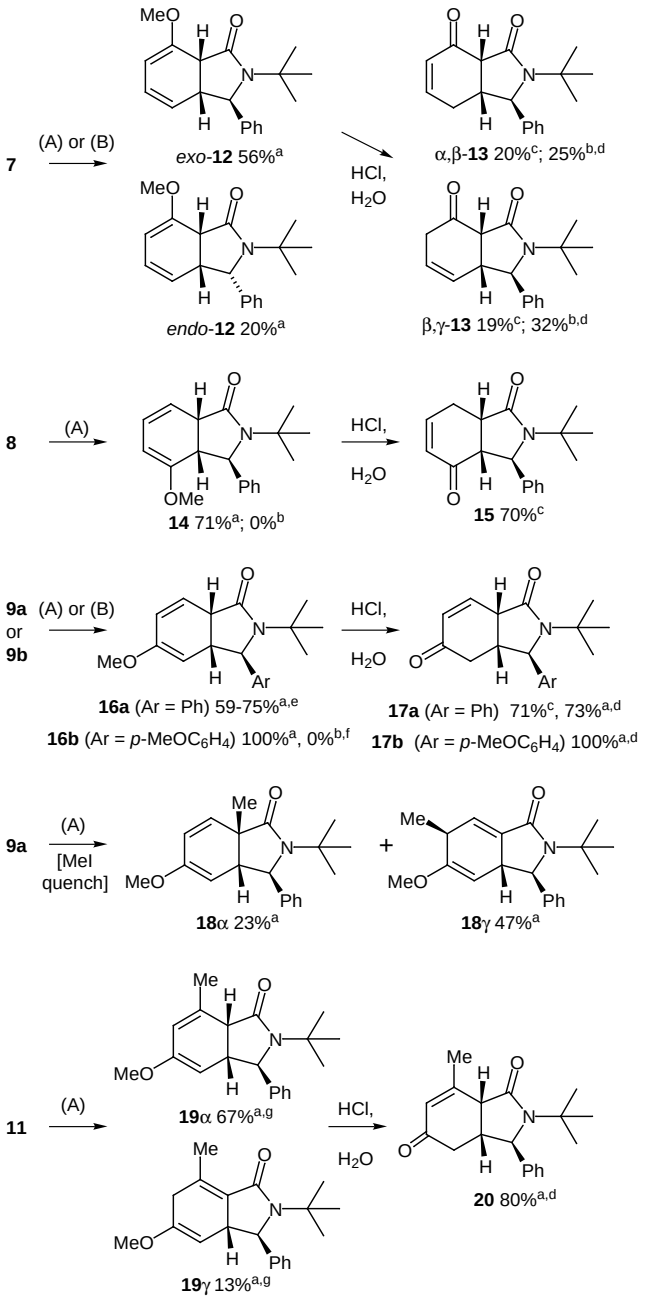
The dearomatised products *exo*-**12**, **14**, **16a**, **16b** and **19** were hydrolysed by treatment with dilute hydrochloric acid, yielding the enones **13** (39%), **15** (70%) and **17a** (71%) **17b** (100%) and **20** (80%). Except in one case − that of **13** − single regioisomers of enones were obtained even from regioisomeric mixtures of intermediates, solving the problem of lack of regioselectivity in the cyclisation step. Curiously, enone **13** was obtained as a mixture of α,β- and β,γ-unsaturated regioisomers. The hydrolysis product from *endo*-**12** was not isolated.

Since our original publication on the cyclisation,[3] we have found that LDA also promotes the cyclisation of *N*-benzyl amides, provided the lithiated intermediate is warmed to 0 °C or above, avoiding the need for the use of toxic HMPA.[8] The three amides **7**, **8** and **9b** were therefore additionally treated with LDA at 0 °C and allowed to warm to room temperature (Method B). Method B improved the yields of the enones **13**, but failed to yield cyclisation products with the less reactive amide **8**. Treatment with LDA caused decomposition of **9b** to the secondary amide **10**.



16aγ

The stereo- and regiochemistry of enone **15** was proved by X-ray crystal structure, shown in the Figure. We have found the preferred ring-junction stereochemistry to be *cis* in all dearomatising cyclisation reactions of benzamides. The regiochemistry of **15** is interesting since the alternative cyclisation (onto the 6-position of lithiated **8**) would produce a less sterically hindered product: presumably the MeO group directs attack into the 2-position by some form of coordination in the transition state of the cyclisation. A similar Li-OMe coordination may be the cause of the loss of stereoselectivity in the cyclisation of **7**.



Scheme 3 Dearomatising Anionic Cyclisation of *N*-Benzylanisamides. (A) 1. *t*-BuLi, THF, HMPA, −78 °C (−40 °C for **8** and **11**), 2. NH_4Cl, H_2O *or* 2. MeI (leading to **18**); (B) 1. LDA, THF, 0-20 °C, 2. NH_4Cl, H_2O. [a]Using method A; [b]Using method B; [c]Yield from isolated cyclised intermediate enol ether; [d]Yield over two steps (one pot) from uncyclised amide; [e]0-12% **16a**γ also obtained; [f]The only product isolated from reaction of **9b** with LDA was **10**; [g]**19**α and **19**γ formed in 5:1 ratio but not isolated.

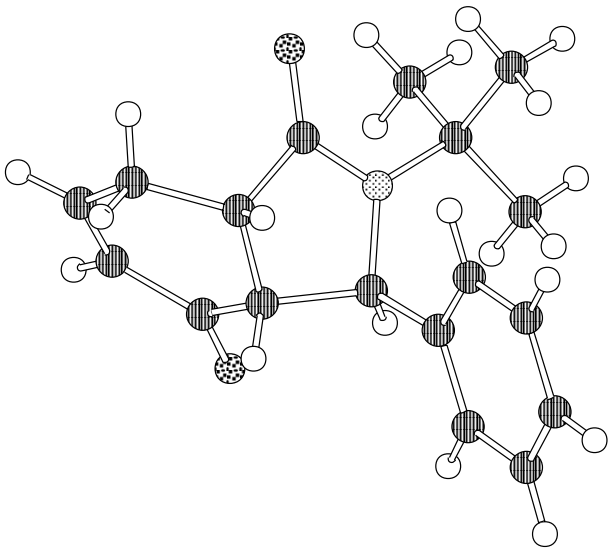
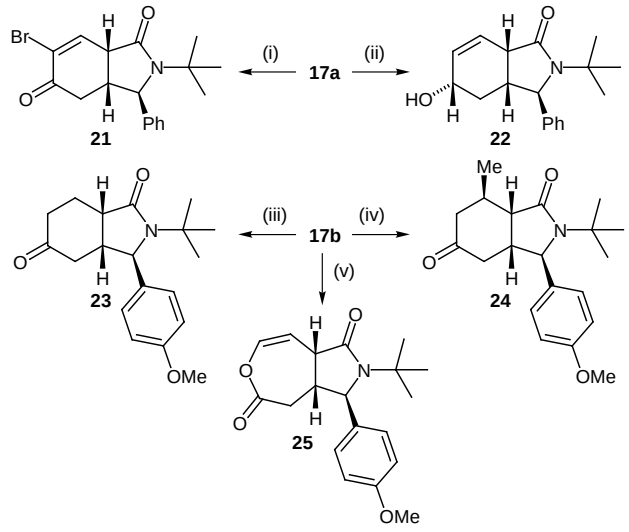


Figure X-ray crystal structure of **15**

The enone products have great potential for further applications in synthesis, and we have already demonstrated the use of a compound related to **17a** as an intermediate in the synthesis of (±)-kainic acid.[4] Scheme 4 illustrates some of the simple transformations which enones **17a** and **17b** readily undergo. Bromination of **17a** followed by elimination gave the bromide **21**. Reduction of the enone in the presence of $CeCl_3$[9] gave a single diastereoisomer of the allylic alcohol **22**, while hydrogenation of **17b** gave **23**. Addition of lithium dimethylcuprate to **17b** in the presence of Me_3SiCl gave a silyl enol ether which hydrolysed to a single diastereoisomer of the ketone **24**,[4] while Baeyer-Villiger oxidation of the enone[10] **17b** gave the versatile enol lactone **25**.



Scheme 4 Transformations of a pyrrolidine-fused enone. (i) Br_2, Et_3N, 50%; (ii) $NaBH_4$, $CeCl_3$, 67%; (iii) H_2, Pd/C (12 mol%), 86%; (iv) 1. Me_2CuLi, Me_3SiCl; 2. HCl, H_2O, 90%; (v) *m*-CPBA, CF_3CO_2H, CH_2Cl_2, 55%.

Typical Procedure

A solution of *tert*-butyllithium (1.3 equiv. of a 1.7 M solution in pentane) was added dropwise to a stirred solution of the amide **9a** (785 mg; 2.64 mmol) and HMPA [TOXIC] (2.75 mL; 15.8 mmol; 6 equiv.) in THF (20 mL) at −78 ºC under nitrogen. After 16 h at −78 °C, dilute HCl (10 mL) was added, and the mixture was allowed to warm to room temperature and stirred for 1 h. The layers were separated, and the aqueous phase was extracted three times with ether. The combined extracts were washed with sodium bicarbonate solution, water and brine, and dried ($MgSO_4$). Evaporation under reduced pressure gave a crude product which was purified by flash chromatography to yield the enone **17a** (546 mg, 73%).

Acknowledgement

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References and Notes

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(6) The stereochemistry of the major product *exo*-**12** and all other cyclisation products was assigned by noting the similarity of the coupling constants of the protons around the pyrrolidinone ring to those of compounds of known stereochemistry (see ref. 3, 4). Our assignment of the stereochemistry of *endo*-**12** is more tentative, and is based on the fact that the coupling $^3J_{NCHCH}$ (6.5 Hz) is very different from the same coupling (0 Hz) in *exo*-**12**, while the ring junction couplings $^3J_{CHCHC=O}$ are similar in the two diastereoisomers (9 Hz and 13 Hz).
(7) The occasional formation of up to 12% of regioisomer **16a**γ seemed to depend capriciously on the fine details of the work-up, and in most cases only **16a** was isolated from this reaction.
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