Dearomatising cyclisations of lithiated *N*-benzylbenzamides

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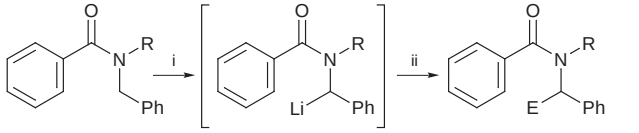
On treatment with Bu^{t}Li in the presence of HMPA, *N*-benzylbenzamides undergo anionic cyclisation with dearomatisation to give an extended amide enolate which reacts with electrophiles to yield bicyclic cyclohexadiene derivatives.

Dearomatisation is an attractive strategy for the synthesis of functionalised six-membered ring compounds,[1] and the Birch reduction has long been the most important dearomatising reaction of substituted benzene rings.[2] More recent methods include addition to chromium–arene complexes, oxidations wtih *Pseudomonas putida*,[3] MAD-promoted nucleophilic attack on aromatic aldehydes and ketones,[4] or radical cyclisation.[5] We have recently described a dearomatising anionic cyclisation of naphthalenes, in which a lithiated tertiary 1-naphthamide undergoes intramolecular attack on the naphthalene ring to generate a benzo[*e*]isoindolinone.[6] We now report that similar conditions promote the dearomatising cyclisation of simple benzamides to give tetrahydroisoindolones.

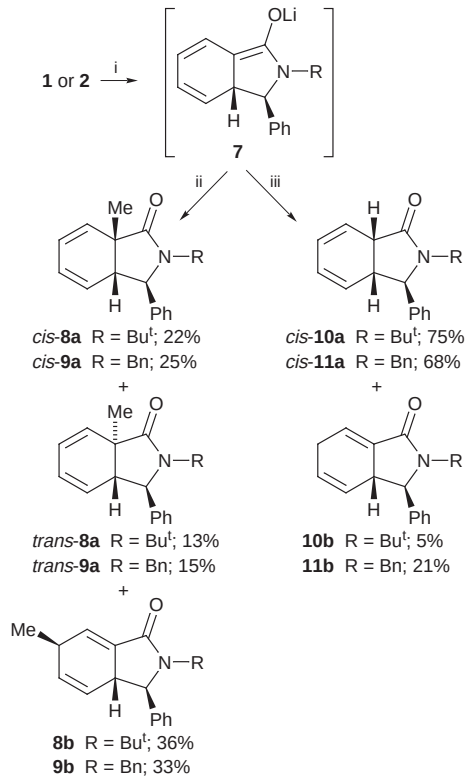
N-Benzylbenzamides **1** and **2** undergo benzylic deprotonation (α to nitrogen) on treatment with Bu^{t}Li, and the α-lithiated species can be alkylated with MeI or BnBr to yield **4**–**6** (Scheme 1).[7] When we carried out this deprotonation in the presence of HMPA, the organolithium **3** was no longer stable over a period of hours at −78 °C, and slowly underwent a new kind of dearomatising anionic cyclisation.[8] Adding MeI after 16 h gave no **4** or **6**, but instead a regio- and stereo-isomeric mixture of cyclised isoindolinones **8** or **9** in 71–73% yield (Scheme 2). In a similar manner, an aqueous quench provided tetrahydroisoindolones **10** and **11**, which are surprisingly resistant to air oxidation, in yields of 80–89%.

At least 6 equiv. of HMPA are essential for high-yielding cyclisations at −78 °C: in pure THF the organolithium **3** (R = Bn) survived for 16 h and returned **2** in quantitative yield upon aqueous quench. DMPU (*N*,*N*'-dimethylpropyleneurea) can be used in place of HMPA, but acceptable yields are then obtained only if the temperature is raised to −40 °C for the 16 h period. TMEDA fails to promote the cyclisation. Organolithium cyclisations are often faster in the presence of lithium-coordinating additives such as HMPA, DMPU or TMEDA:[9] these are assumed to work by promoting dissociation of the organolithium to an ion pair.[10] It would then be the ion pair which cyclises, by a mechanism which is as yet unclear, but may be electrocyclic. Besides our naphthamide cyclisation,[6] there



1 R = Bu^t
2 R = Bn
3
4 R = Bu^t, E = Me; 96%
5 R = Bu^t, E = Bn; 80%[a]
6 R = Bn, E = Me; 45%[b]

Scheme 1 *Reagents and conditions*: i, Bu^{t}Li (3 equiv.), THF −78 °C, 6 h; ii, MeI or BnBr. [a] HMPA added 5 min before BnBr. In the absence of HMPA, only starting material was recovered. [b] Deprotonated in presence of HMPA (−78 °C, 20 min). Remainder consists largely of cyclised material as described below.



Scheme 2 *Reagents and conditions*: i, Bu^{t}Li (1.3 equiv.), HMPA (6 equiv.), THF, −78 °C, 16 h; ii, MeI; iii, H_2O.

are few precedents for cyclisation of an organolithium onto an aromatic ring,[11] and only one which results in loss of aromaticity.[12] Curran has described a closely related radical cyclisation of an *N*-benzyl-*N*-*tert*-butylbenzamide[13] which yields a rearomatised isoindolone.

Whatever the detailed mechanism of the cyclisation, it must produce the extended enolate **7**, with the phenyl group lying *exo* to the 6,5-fused ring system. Enolate **7** evidently reacts both α and γ to the amide carbonyl group,[14] leading to the observed mixture of regioisomers.† We observed only one stereoisomer of the γ-alkylated compounds **8b**–**11b**; we assigned their stereochemistry by means of an X-ray crystal structure of **8b**

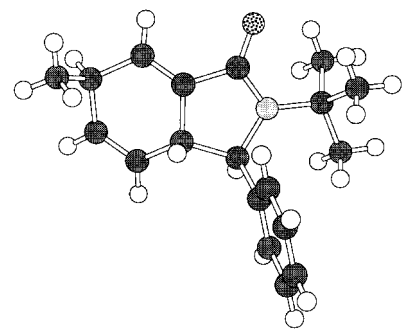


Fig. 1 X-Ray crystal structure of **8b** (R = Bu^t).

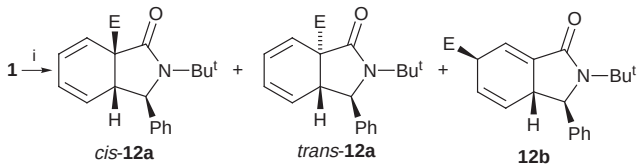
Table 1 Cyclisation results with various electrophiles

Entry	E^+	E	Yield (%)[a] **12** (total)	*cis*-**12a**	*trans*-**12a**	**12b**	α : γ ratio **12a** : **12b**[b]	*cis*-**12a**: *trans*-**12a**[b]
1	NH_4Cl	H	80[c]	75	0	5	3.5 : 1	> 20 : 1
2	MeI	Me	71[d]	22	13	36	1 : 1	1.3 : 1
3	MeOTs	Me	56[d]	43	5	8	7 : 1	6 : 1
4	MeOTf	Me	47[d]	34	13	0	20 : 1	2 : 1
5	allyl-Br	allyl	73	46	0	27	3 : 1	> 4 : 1
6	BnBr	Bn	65	61	0	4	1.6 : 1	> 20 : 1
7	EtI	Et	11	—	—	—	*ca.* 1 : 1	—
8	EtOTs	Et	30	30	0	0	*ca.* 6 : 1	> 20 : 1

[a] Isolated yield. [b] Ratio by ^{1}H NMR analysis. [c] **12** (E = H) is identical with **10**. [d] **12** (E = Me) is identical with **8**.

(Fig. 1), which shows the cyclohexadiene ring as a boat bearing the methyl group pseudoaxially.‡ The α-alkylated compounds **8a** and **9a** were formed as stereoisomeric mixtures, with the *cis* ring junction favoured (as in the related naphthamide series[6]). Their relative stereochemistry was elucidated by NOE studies. The major stereoisomers are formed by attack of the electrophile on the *exo* face of the bicyclic enolate **7**.

The same three classes of products, in varying ratios, were obtained when other electrophiles were used to quench the cyclisation, as shown in Scheme 3 and Table 1. Harder alkylating agents apear to favour α-attack on **6** (MeOTf > MeOTs > MeI); more sterically demanding alkylating agents appear to be more stereoselective.



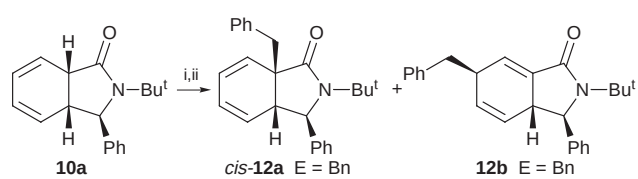
Scheme 3 *Reagents and conditions*: i, Bu^{t}Li (1.3 equiv.), HMPA (6 equiv.), THF, −78 °C, 16 h; ii, E^+.

It was also possible to improve the regioselectivity of the alkylation step by varying the enolate counterion or solvent. Table 2 shows the result of reforming the enolate **7** with Bu^{s}Li, LiHMDS, NaHMDS or KHMDS, and alkylating it with BnBr (Scheme 4). The lithium enolate generated by deprotonation with Bu^{s}Li reacts more regioselectively than the same enolate formed by the reaction in the presence of HMPA, and the presence of hexamethyldisilazane leads almost solely to the α-alkylated product. The sodium and potassium enolates reacted less regioselectively, but the potassium enolate gave an almost quantitative yield of isolated regioisomers.

Table 2 Alkylations using various bases

Entry	Base	Yield (%)[a] *cis*-**12a** (E = Bn)	**12b** (E = Bn)	α : γ ratio **12a** : **12b** (E = Bn)[b]
1	Bu^{s}Li	57[c]		3 : 1
2	LiHMDS	70	7	10 : 1
3	NaHMDS	39	21	3.5 : 1
4	KHMDS	75	17	4 : 1

[a] Isolated yield. [b] By ^{1}H NMR analysis. [c] Isolated yield of mixture.



Scheme 4 *Reagents and conditions*: i, base (2 equiv.); ii, BnBr.

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Notes and references

† The ratio of **10a** : **10b** is kinetically controlled: **10a** and **10b** do not interconvert under the conditions of the aqueous work-up, nor even in Bu^{t}OK–Bu^{t}OH at 80 °C.

‡ *Crystal data* for **8b**: colourless plates, $C_{19}H_{23}NO$, triclinic, space group *P*1, *a* = 8.316(1), *b* = 15.316(2), *c* = 6.424(2) Å, α = 93.10(2), β = 92.74(2), γ = 79.96(1)°, 3491 reflections measured, 3273 unique, *R* = 0.068, R_w = 0.055. CCDC 182/1112.

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