From Diketopiperazines to Hydantoins: An Unprecedented Rearrangement

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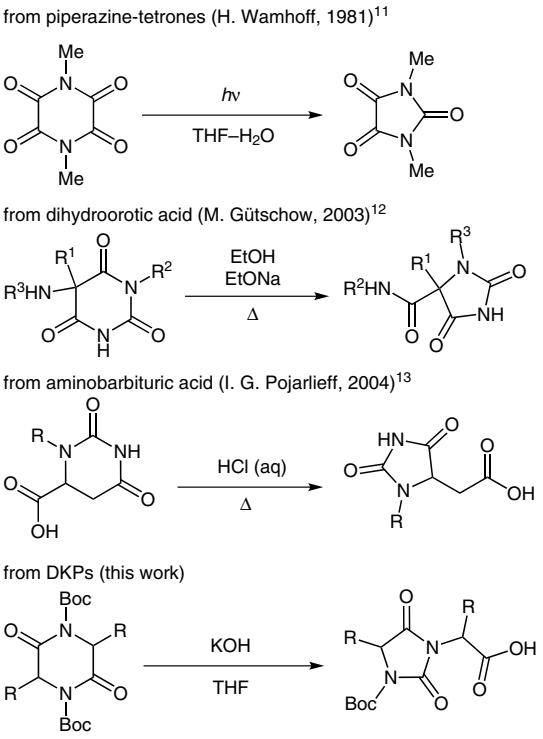
Abstract: Bis-Boc-activated 2,5-diketopiperazines on reaction with potassium hydroxide or sodium methoxide in dry tetrahydrofuran led to Boc-protected hydantoins through an unprecedented ring contraction. This rearrangement was applied to several monosubstituted 2,5-diketopiperazines with good yields and regioselectivity.

Key words: ring contraction, rearrangement, heterocycles, lactams, amino acids

In the field of bioorganic chemistry, considerable attention has been paid to diketopiperazines (DKP)[1,2] and hydantoins[3] as biologically active scaffolds, targets in combinatorial chemistry for the discovery of lead structures, or motifs for building foldamers.[4] Hydantoin and DKP skeletons are used for adding or suppressing a methylene unit in analogues to affect their pharmacological recognition and biological properties.[5–7] The literature reveals a plethora of studies emphasizing the strong chemical and biological impact of both aza-heterocycles, raising them to the status of 'privileged scaffolds' in medicinal chemistry.[8,9] Furthermore, Menéndez et al. recently classified DKP moieties as 'privileged scaffolds in synthesis' as critical starting materials for other heterocyclic systems.[2] However, to the best of our knowledge, no mention has been made of direct hydantoin synthesis from DKP rearrangement.

So far, the closest reactions described in literature are the photorearrangement of 1,4-dimethylpiperazine-2,3,5,6-tetrones to dimethylimidazolidinetriones,[10] the aminobarbituric acid–hydantoin rearrangement[11] and the transformation of dihydroorotic acid to hydantoinic acid[12] (Scheme 1). We present in this study a simple and yet unprecedented rearrangement allowing the synthesis of functionalized hydantoins from suitable Boc-activated 2,5-diketopiperazines. The regio- and stereocontrol of the reaction is also discussed.

Boc-activated DKP were rarely considered as starting materials. They were essentially described as precursors of peptidic pyrrolidines or as ring-contraction substrates leading to pyrrolidine-2,4-dione systems via a transannular rearrangement of activated lactams (TRAL).[13–17] The reactivity of Boc-DKP centers around the conversion of a lactam group into a more activated pseudo-imide moiety.



Scheme 1 Six-to-five-membered ring rearrangements: access to hydantoin skeletons

Hence, the *N*-*tert*-butoxycarbamate is no longer acting as a protecting group but as an electrophilic activator of the lactam function.[18–20] More generally, it is well-known that conversion of an amide moiety into its *N*-Boc derivative leads selectively to the hydrolysis of the amide, with preservation of the *N*-Boc group, in the presence of a hydroxide source.[21,22]

While the weakly nucleophilic potassium *tert*-butoxide acted on bis-Boc cyclo[Gly-Val] (**1**) as a strong base leading to the TRAL product, the use of a KOH suspension initiated a different rearrangement, smoothly providing the hydantoin **8**.[23] The ring-contracted product was isolated with an excellent yield and total regioselectively, but as a mixture of enantiomers (*S*)-**8** and (*R*)-**8** with a modest enantiomeric ratio (Table 1, entry 1).[24]

A simple acid–base extraction of the crude reaction mixture allowed the clean separation of hydantoins **8** from the unreacted DKP **1** which can then be recycled to provide a quantitative yield.

As expected, reproducible results were observed with the enantiomer **2** (Table 1, entry 2), which permitted us to de-

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