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A New Strategy for the Preparation of Secondary Amines via *o*-(Tetrahydropyranloxymethyl)-benzamides

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Abstract:

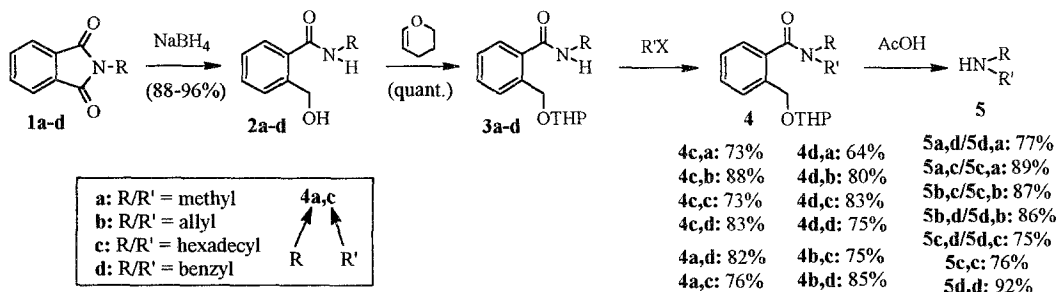
The new synthesis strategy for the preparation of secondary amines starts from *N*-alkyl-phthalimides which are reduced to the corresponding *o*-hydroxymethyl-*N*-alkyl-benzamides. After protection of the hydroxy group as tetrahydropyranyl ether the *N*-alkyl-benzamides are alkylated to *o*-(tetrahydropyranloxymethyl)-*N,N*-dialkyl-benzamides. The deprotection of the hydroxy group and the release of the secondary amines can be achieved in excellent yields in one reaction step using aqueous acetic acid. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: synthesis; secondary amines; phthalimides; protecting groups; deblocking conditions

One major problem of synthesis of secondary amines by simple alkylation of primary amines is the formation of tertiary amines and/or quaternary ammonium salts. To overcome this problem secondary amines are usually synthesized by alkylation of monoalkylated trifluoroamides, sulfonamides or benzylamines [1-12]. Releasing of the secondary amines requires often harsh deprotection conditions.

Here we present a new synthesis strategy for the preparation of secondary amines starting from *N*-alkyl-phthalimides (scheme). The synthesis is based on a procedure to convert *N*-alkyl-phthalimides to primary amines described by Osby et al. [13]: *N*-alkyl-phthalimides were reduced with NaBH₄ to *o*-hydroxymethyl-*N*-alkyl-benzamides. Afterwards the release of the primary amines was performed by treatment with acetic acid.

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The synthesis of secondary amines described here also starts from N-alkyl-phthalimides which can be obtained by numerous methods, e.g. by treatment of primary amines with phthalic anhydride, by N-alkylation of phthalimide or by N-alkylation via Mitsunobu reaction [14, 15].

We have alkylated phthalimide with methyl iodide (a), allyl bromide (b), hexadecyl mesylate (c) and benzyl chloride (d) (1.2eq) using potassium *tert*-butylate (1.2eq) as base to give the corresponding N-alkyl-phthalimides **1a-d** (DMF, rt., 1h, quant.). **1a-d** were reduced with an excess of NaBH₄ (3eq) in 2-propanol/toluene/water (6:1:1) at 0°C (4h) to yield the o-hydroxymethyl-N-alkyl-benzamides **2a-d**. The o-(tetrahydropyranoxymethyl)-N-alkyl-benzamides **3a-d** were obtained by reaction of **2a-d** with dihydropyran (5eq) and a catalytic amount of p-toluene sulfonic acid (dichloromethane, rt., 2h) [16]. The o-(tetrahydropyranoxymethyl)-N-alkyl-benzamides **3a-d** were deprotonated with potassium *tert*-butylate (1.2eq) and alkylated using the same alkylation reagents (1.2eq) mentioned above (DMF, 40°C, 6h) to give the corresponding o-(tetrahydropyranoxymethyl)-N,N-dialkyl-benzamides **4**. The release of the secondary amines **5** was achieved by warming solutions of the compounds **4** in a mixture of acetic acid, tetrahydrofuran and water (4:2:1) in good yields (60°C, 4h). These acidic conditions enable both the removal of the tetrahydropyranyl group and afterwards the release of the secondary amines of which the deprotected hydroxy group serves as prerequisite.

The new synthesis strategy for the preparation of secondary amines bearing two different alkyl residues can be generally applied in two different ways. On the one hand the synthesis could start from the alkylated phthalimides which allow the conversion into secondary amines. On the other hand the synthesis could start from compounds bearing a leaving group (R'X in scheme) which can be substituted by preformed o-(tetrahydropyranoxymethyl)-N-alkyl-benzamides **3**. This second way can be used to introduce various N-alkyl-amines into molecules under mild conditions.

We hope that this new synthesis strategy for the preparation of secondary amines will find wide applications due to the excellent yields and the advantage of the very mild acidic deprotection conditions for releasing the secondary amines.

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