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An Expeditious Synthesis of Cyclic Imides

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Abstract: Trifluoroacetamide was reacted with diacids in the presence of N-ethyl-N-dimethylaminopropylcarbodiimide and of 1-hydroxybenzotriazole to afford cyclic imides of different ring size, providing a single step asymmetric synthesis of thalidomide. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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Glutarimides possess numerous biological activities, i.e. thalidomide has recently received agreement as an antiHIV agent.[1] The antiaromatase agent aminoglutethimide is used against œstrogeno-dependent cancers.[2] Some other glutarimide derivatives are muscarinic agonists[3] and an anticonvulsant activity has been reported for benzyloxycarbonylaminoglutarimide.[4] The preparation of cyclic imides depends on the ring size: the five-membered rings are easily obtained and their formation is a frequent side reaction in the chemistry of asparagine.[5] Glutarimides are in most cases prepared by cyclisation of nitrile esters in the presence of acids,[6] or by cyclisation of monoamides in the presence of thionyl chloride[7] or BOP.[8] The seven-membered analogs are formed in low yield by heating dinitriles in strongly acidic conditions.[9] We have previously developed a mild three-step synthesis of glutarimide derivatives.[10] It relies on the formation of 1-benzyloxyglutarimides followed by the removal of the benzyloxy group. We wish to report a one-step simple and general route to cyclic imides **2**.

2 (Yield in %)	**a** (58)	**b** (81)	**c** (92)	**d** (83)	**e** (75)
mp °C	141-143	122-123	188-189	137-139	270
(Lit.)	139-144[14]	120-121[15]	193[16]	141-142[17]	269[10a]

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It is based on the condensation of the diacids **1** with trifluoroacetamide in the presence of N-hydroxybenzotriazole (HOBt) and N-(3-dimethylamino)propyl-N-ethylcarbodiimide hydrochloride (EDCCl).[11] Other condensation agents were investigated e.g.: dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC) but the yields were low. The monitoring of the reaction by tlc showed that the reaction proceeded rapidly even below room temperature. The N-trifluoroacetyl intermediate was not enough stable to be detected in the reaction medium, presumably due to a nucleophilic attack of the benzotriazolate anion.

From a practical point of view, this process is also advantageous since all the side products are eliminated during work-up. The enantiomeric purity of chiral derivatives **2b,e** was checked by chiral-HPLC.[12] Clearly, the cyclisation conditions did not induce racemization of the stereogenic centers. Racemic aminoglutethimide was obtained by catalytic hydrogenation of **2d**.[13] This mild and efficient protocol is fast and gives products cleanly. It was applied to various ring sizes and could be useful for the preparation of new therapeutic agents.

References and notes

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11. A general experimental procedure is as follows: Trifluoroacetamide (1.13 g, 10 mmol) was added to a solution of diacid (10 mmol) (**1a-e**), 1-hydroxybenzotriazole (2.90 g, 22 mmol) and triethylamine (4.20 mL, 30 mmol) in 30 mL CH_2Cl_2 at 0°C. N-(3-Dimethylamino)propyl-N-ethyl carbodiimide hydrochloride (4.0 g, 21 mmol) was added and the mixture was allowed to reach room temperature. After 1 h stirring, water (20 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was washed twice with 2 N Na_2CO_3 (50 mL) then with water, dried and evaporated. The products could be recrystallized from ethyl acetate. They were all characterized by ^1H and ^{13}C-RMN. In particular, the ^{13}C spectra showed signals at δ($CDCl_3$, TMS) =165-169 ppm for C=O imide-groups.
12. Chiral HPLC were performed on a Chiracel OJ (25 cm x 4.6 mm) column (Daicel, Tokyo) connected with a UV photodiode array detector(Waters 994) at 220 nm and a polarimetric detector Jasco OR 990. The mobile phase was constituted of absolute ethanol with a flow rate 1 $mL.mn^{-1}$. The S enantiomers were eluted first. Ee of crude products before recrystallization: **2b**: ee = 96%, **2e**: ee = 88%.
13. Catalytic hydrogenation was performed at atmospheric pressure by stirring **2d**(2.6 g, 10 mmol) and 5% Pd-C (0.1 g) in 30 mL ethanol. Absorption of hydrogen ceased after 1 h. Yield: 95 %.
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