

## An Expedient Synthesis of Cyclic Imides

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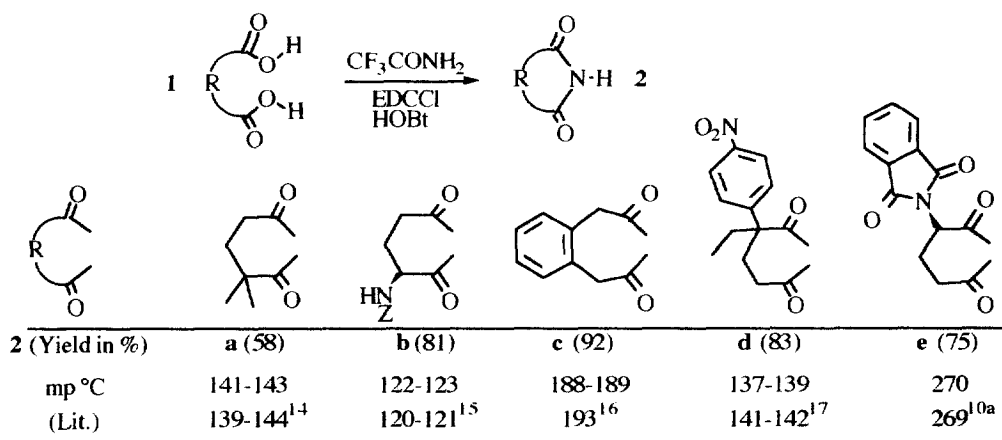
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**Abstract:** Trifluoroacetamide was reacted with diacids in the presence of N-ethyl-N-dimethylaminopropylcarbodiimide and of 1-hydroxybenzotriazole to afford cyclic imides of different ring size, providing a single step asymmetric synthesis of thalidomide. © 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.<sup>1</sup> The antiaromatase agent aminoglutethimide is used against œstrogeno-dependent cancers.<sup>2</sup> Some other glutarimide derivatives are muscarinic agonists<sup>3</sup> and an anticonvulsant activity has been reported for benzyloxycarbonylamino glutarimide.<sup>4</sup> 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.<sup>5</sup> Glutarimides are in most cases prepared by cyclisation of nitrile esters in the presence of acids,<sup>6</sup> or by cyclisation of monoamides in the presence of thionyl chloride<sup>7</sup> or BOP.<sup>8</sup> The seven-membered analogs are formed in low yield by heating dinitriles in strongly acidic conditions.<sup>9</sup> We have previously developed a mild three-step synthesis of glutarimide derivatives.<sup>10</sup> 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**.



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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 (EDCC).<sup>11</sup> 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 benzotriazolone 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.<sup>12</sup> Clearly, the cyclisation conditions did not induce racemization of the stereogenic centers. Racemic aminoglutethimide was obtained by catalytic hydrogenation of **2d**.<sup>13</sup> 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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- 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<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub> (20 mL) were added. The organic layer was washed twice with 2 N Na<sub>2</sub>CO<sub>3</sub> (50 mL) then with water, dried and evaporated. The products could be recrystallized from ethyl acetate. They were all characterized by <sup>1</sup>H and <sup>13</sup>C-RMN. In particular, the <sup>13</sup>C spectra showed signals at δ(CDCl<sub>3</sub>, TMS) = 165-169 ppm for C=O imide-groups.
- 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.min<sup>-1</sup>. The S enantiomers were eluted first. Ee of crude products before recrystallization: **2b**: ee = 96%, **2e**: ee = 88%.
- 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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