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A novel tandem process leading to functionalized glutarimides

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Abstract—The synthesis of various functionalized or spirobicyclic glutarimides by a novel tandem process has been disclosed. The reaction involves a base-catalyzed Michael addition of active methylene compounds to secondary conjugated amides, followed by intramolecular *N*-acylation of the carboxamido group. It provides a relatively general and simple access to useful synthetic intermediaries and potentially active pharmacological compounds. In addition, a novel group of spirobicyclic systems has been synthesized.

Cyclic imides, especially five- and six-membered systems, are useful chiral and achiral precursors in the synthesis of lactams,[1] pyrrolidines,[2] piperidines,[3] alkaloids,[4] and open-chain compounds.[5] In addition, *N*-acyliminium ions, a highly versatile class of synthetic intermediaries, are best prepared from cyclic imides.[6] Macrocyclic imides have been prepared from cyclic β-keto esters and alkyl isocyanates.[7] Substituted imide rings are also found in some pharmacologically active natural products, such as cycloheximide,[8] sesbanimide,[9] and migrastatine.[10] Numerous compounds possessing a cyclic imide moiety exhibit pharmacological activity such as antitumor (e.g., sesbanimide,[9] migrastatine,[10] glutethimide,[8] aminoglutethimide[8]), immunosuppressive, and sedative (e.g., thalidomide[8]), anxiolytic (e.g., buspirone[8]), anticonvulsive,[11] and others.[12]

Although glutarimide rings are usually formed in a separate synthetic step from various precursors,[9,13] there are several tandem reactions combining C–C and C–N bond formation. In most cases the first step involves Michael addition of active methylene compounds (malondiamides,[3] *N*-alkyl-malonamic acid esters,[14] cyano-acetates,[15] arenesulfonylacetates[16]) to conjugated esters, or nitriles. In the second step the ring is formed via intramolecular *N*-acylation. Interestingly, conjugated amides have not been examined as Michael acceptors, with the single exception of methacrylamide when two 3-substituted glutarimides were prepared in the presence of CsF/Si(OMe)$_4$.[17]

Herein we report a novel tandem process leading to various functionalized or spirobicyclic glutarimides. The method involves a base-catalyzed Michael addition of active methylene compounds to secondary acrylamides or crotonamides, followed by intramolecular *N*-acylation of the carboxamido group (Scheme 1 and Table 1). Initially, we examined the reaction of dimethyl malonate **1a** and *N*-phenethylacrylamide **2a** under various conditions. When the reaction was performed in the presence of potassium *t*-butoxide and 18-crown-6, spirobisglutarimide **3a** was isolated in variable yields, Scheme 1A. Optimization of the reaction included variation of the base (10–400 mol% of NaH, MeONa, MeOLi, LiH, anhyd K_2CO_3, anhyd KF, Bu_4NF, *t*-BuOK, DBU), phase-transfer catalysts (10–30 mol% of TEBA, Aliquat 336, 18-crown-6), solvent (hexane, heptane, toluene, acetonitrile, THF, *t*-butanol, *t*-pentanol, *i*-propanol, *n*-propanol, ethanol, methanol, DMSO, DMF), and temperature (20–100 °C). Generally, the reaction requires polar and protic, but non-nucleophilic solvents (e.g., tertiary-alcohols), a phase-transfer catalyst and a non-nucleophilic base.

The presence of atmospheric oxygen apparently has an adverse effect, at least in some cases. A combination of *t*-BuOK (~50 mol%), 18-crown-6 (15 mol%), and

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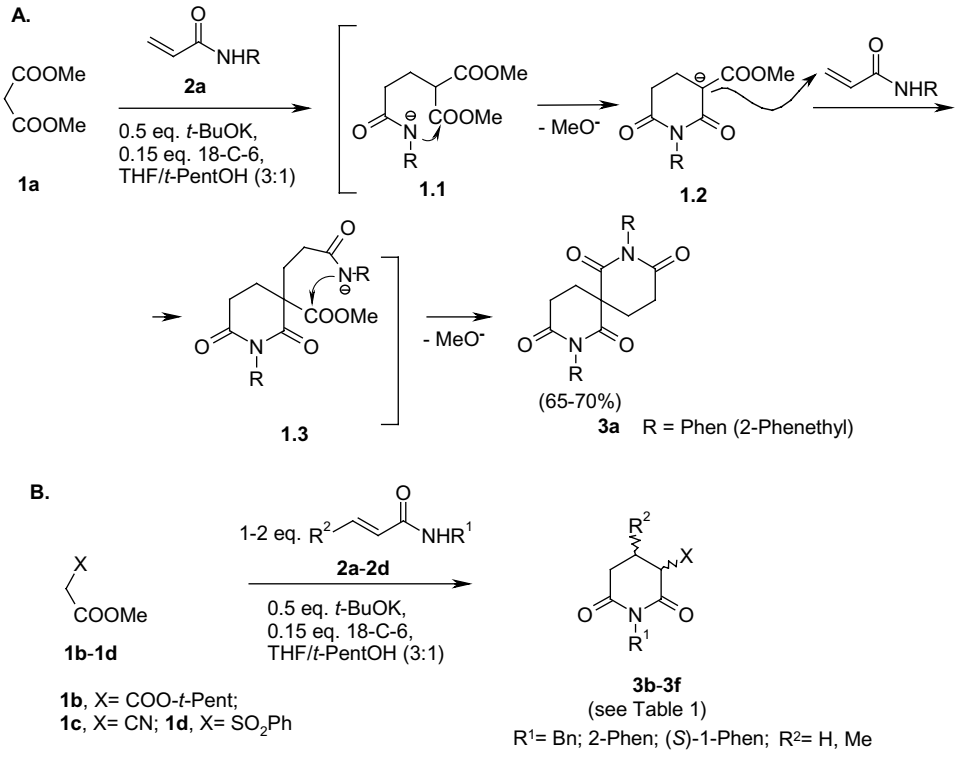
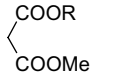
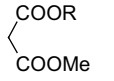
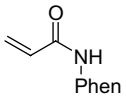
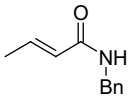
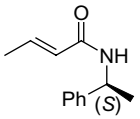
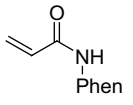
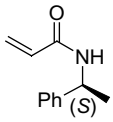
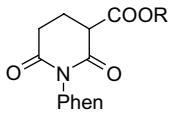
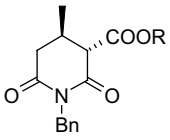
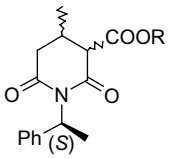
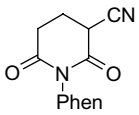
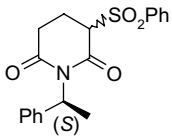
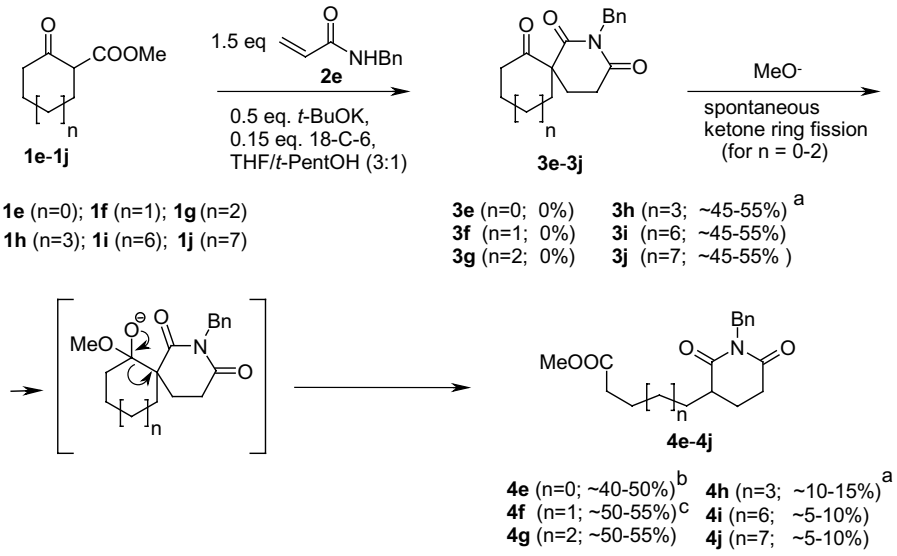


Scheme 1.

Table 1. 3-Substituted glutarimides (**3b**–**3f**) from the tandem reaction of active methylene compounds (**1b**–**1d**) and conjugated amides (**2a**–**2d**)

 **1b** R = *t*-pentyl	 **1b**	 **1b**	 **1c**	 **1d**
 **2a**	 **2b**	 **2c**	 **2a**	 **2d**
 **3b** (45–55%)	 **3c** (45–55%) (2 isomers, 1:9[19])	 **3d** (35–45%) (2 isomers, 1:1[19])	 **3e** (60–72%)	 **3f** (45–50%) (2 isomers, 1:1[19])

THF/*t*-pentanol (3:1) at ~70 °C/3 h was found to be optimal. Interestingly, anhyd K_2CO_3, also promoted cyclization, although less efficiently than *t*-BuOK. Other catalyst/solvent combinations were much less effective or ineffective. The application of these reaction conditions to other active methylene compounds such as methyl-*t*-pentyl malonate **1b**, ethyl-2-cyanoacetate **1c** and ethyl-2-(phenylsulfonyl)acetate **1d** furnished 3-substituted glutarimides **3b**–**3f** in 35–72% yields (Scheme 1B and Table 1).[18] Surprisingly, methyl-*t*-butyl malonate gave lower yields (35–40%) of the corresponding glutarimide derivative than **1b**. As expected, good diastereoselectivity (presumed *trans*) was achieved with amides **2b** (glutarimide **3c**, estimated *cis*/*trans* ratio 1:9[19]) and **2c** (glutarimide **3d**, two isomers in a 1:1 ratio[19]), Table 1. Since the methine C–H bond in glutarimides **3b**–**3f** is highly enolizable, no stable stereocenter could be generated in that position.



Scheme 2. [a]Isolated yields from several runs, after dry-flash chromatography; [b]the ethyl ester analogue of **4e** was also prepared; [c]two analogues of **4f** were also prepared.

However, the course of the reaction with cyclic β-keto esters,[20] depends crucially upon the ring-size of the reactant, Scheme 2.

Thus, β-keto esters possessing 5–7 membered rings (**1e**–**1g**) afforded only 3-substituted glutarimides **4e**–**4g**, originating from the spontaneous alkoxide-induced ketone ring fission in the last step, Scheme 2. Similarly, methyl-5-*t*-butyl-2-oxocyclohexanecarboxylate yielded a glutarimide analogous to **4f**, as a mixture of two diastereoisomers. It is apparent that the intermediate spirobicyclic systems **3e**–**3g** were too unstable under the reaction conditions to be isolated, even at ~20 °C. On the contrary, methyl-2-oxocyclooctanecarboxylate **1h** produced predominantly the spirobicyclic system **3h** at ~20 °C (after 72 h) while at ~70 °C mainly the ring fission product **4h** was obtained. In the case of 11- and 12-membered β-keto esters **1i** and **1j**, the spiroglutarimides **3i** and **j**[21] formed were stable even at ~70 °C and could be isolated as the major products.

The corresponding fission products **4i** and **4j** were formed only in minor amounts (~5–10%).[22] Spectral data for the compounds synthesized (^{1}H NMR, ^{13}C NMR, DEPT, and MS) are given in the Supplementary data.

In conclusion, the present results demonstrate the usefulness of the described tandem process for the synthesis of various functionalized glutarimides and spiroglutarimides. Besides the synthetic significance and potential pharmacological activity of these compounds, spiroglutarimides **3h**–**3j** appear to represent a novel class of substituted glutarimides.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.087.

References and notes

1. (a) Bennett, D. J.; Blake, A. J.; Cooke, P. A.; Godfrey, C. R. A.; Pickering, P. L.; Simpkins, N. S.; Walker, M. D.; Wilson, C. *Tetrahedron* **2004**, *60*, 4491–4511; (b) Chen, C.-Y.; Chang, B.-R.; Tsai, M.-R.; Chang, M.-Y.; Chang, N.-C. *Tetrahedron* **2003**, *59*, 9383–9387, and references cited therein.
2. Ibnusaud, I.; Thomas, G. *Tetrahedron Lett.* **2003**, *44*, 1247–1249.
3. (a) Callewaert, G. Leo. WO 2002068416 A2 ; *Chem. Abs.* *137*:216939; (b) Chang, M.-Y.; Chen, S.-T.; Chang, N.-C. *Tetrahedron* **2002**, *58*, 3623–3628.
4. Yoda, H.; Egawa, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 1643–1646.
5. Oba, M.; Koguchi, S.; Nishiyama, K. *Tetrahedron* **2002**, *58*, 9359–9363.
6. Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.
7. Heerklotz, J.; Linden, A.; Hesse, M. *Tetrahedron* **2000**, *56*, 7205–7210.
8. *The Merck Index*, 13th ed.; Merck & Co.: NJ, 2001.
9. Grieco, P. A.; Henry, K. J.; Nunes, J. J.; Matt, J. E., Jr. *J. Chem. Soc., Chem. Commun.* **1992**, *4*, 368–370.
10. Gaul, C.; Njardarson, J. T.; Shan, D.; Dorn, D. C.; Wu, K.-D.; Tong, W. P.; Huang, X.-Y.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 11326–11337.
11. Dandekar, S. A.; Greenwood, S. N.; Greenwood, T. D.; Mabic, S.; Merola, J. S.; Tanko, J. M.; Wolfe, J. F. *J. Org. Chem.* **1999**, *64*, 1543–1553.

12. Leonardi, A.; Barlocco, D.; Montesano, F.; Cignarella, G.; Motta, G.; Testa, R.; Poggesi, E.; Seeber, M.; De Benedetti, P. G.; Fanelli, F. *J. Med. Chem.* **2004**, *47*, 1900–1918.
13. (a) Mederski, W. W. K. R.; Baumgarth, M.; Germann, M.; Kux, D.; Weitzel, T. *Tetrahedron Lett.* **2003**, *44*, 2133–2136; (b) Osipov, S. N.; Tsouker, P.; Hennig, L.; Burger, K. *Tetrahedron* **2004**, *60*, 271–274.
14. Crowe, D.; Jones, D. A. WO 2001014335 A1; *Chem. Abs.* *134*:207718.
15. (a) Hikaru, T.; Kazunori, Y.; Katsuhiro, I.; Hiroki, T.; Shun-Ichi, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3302–3304; (b) Grossman, R. B.; Pendharkar, D. S.; Rasne, R. M.; Varner, M. A. *J. Org. Chem.* **2000**, *65*, 3255–3258.
16. Chen, C.-Y.; Chang, M.-Y.; Hsu, R.-T.; Chen, S.-T.; Chang, N.-C. *Tetrahedron Lett.* **2003**, *44*, 8627–8630, and references cited therein.
17. Chuit, C.; Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* **1986**, *42*, 2293–2301.
18. All new compounds according to detailed structure and substructure searches of Chemical Abstracts via SciFinder. Structurally related glutarimides were reported previously by other routes, see Refs. 1,3, and 16.
19. From ^{13}C NMR spectra, see Supplementary data.
20. Prepared by a modification of a known literature procedure Krapcho, A. P.; Diamanti, J.; Cayen, C.; Bingham, R. *Org. Synth., Coll.* **1973**, *5*, 198.
21. Typical experimental procedure for **3j**: A solution of methyl-2-oxocyclododecanecarboxylate **1j** (2.0 g, 8.32 mmol), *N*-benzylacrylamide **2e** (2.02 g, 12.5 mmol), *t*-BuOK (0.47 g; 4.16 mmol) and 18-crown-6 (0.33 g, 1.25 mmol) in 10 mL of THF/*t*-PentOH (3:1), was heated and stirred under Ar (70 °C, 3 h). After cooling, the mixture was poured into a buffered solution (3.0 g of KH_2PO_4 in 50 mL H_2O), extracted (CH_2Cl_2, 3×20 mL), dried (anhyd $MgSO_4$), and concentrated. Purification by dry-flash chromatography (SiO_2, hexane:EtOAc, gradient 99:1, etc.) yielded 2-benzyl-2-aza-spiro[5.11]heptadecane-1,3,7-trione **3j** as a pale yellow viscous oil (1.42–1.68 g, 46–55% over several runs). ^1H NMR, ^{13}C NMR, DEPT, and MS spectra are given in the Supplementary data.
22. Structures **3h**–**3j** and **4e**–**4j** are novel compounds and were fully characterized by ^1H NMR, ^{13}C NMR, DEPT, and MS spectra (given in the Supplementary data).