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# An efficient synthesis of *N*-benzyl-3-sulfonyl glutarimides. Formal synthesis of the aromatase inhibitor AG-1

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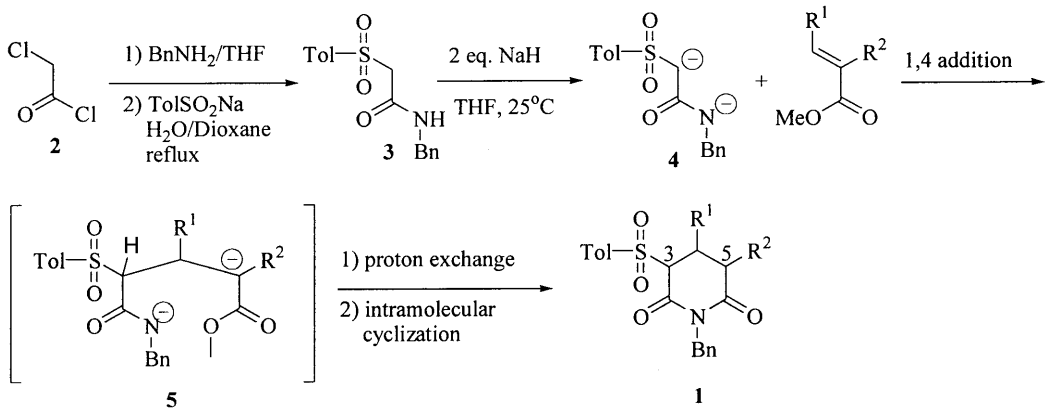
**Abstract**

A formal [3+3] cycloaddition strategy to substituted glutarimides was studied. *N*-Benzyl α-sulfonyl-acetamides and various α,β-unsaturated esters were used as starting materials. 

Glutarimides possess various biological activities.[1] Therefore, the preparation of these cyclic imides has attracted considerable attention from organic chemists.[2] We wish to report an efficient route towards the synthesis of *N*-benzyl-3-sulfonyl-4-or-5-substituted glutarimides **1**. The aromatase inhibitor AG-1 was also synthesized.[3]

Sequential treatment of chloroacetyl chloride with benzylamine and sodium *p*-toluenesulfinate furnished α-toluenesulfonyl acetamide **3** in 90% yield. After reaction of **3** with two equivalents of sodium hydride, the resulting dianion **4** reacted with a variety of α,β-unsaturated esters to afford the corresponding substituted *N*-benzyl-3-toluenesulfonyl glutarimides **1**. Presumably, after 1,4-addition, ring closure of **5** could then follow, providing the cyclized product **1** (Scheme 1).




Scheme 1.

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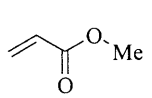
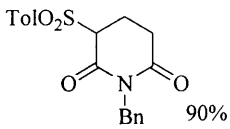
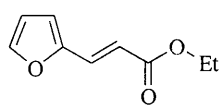
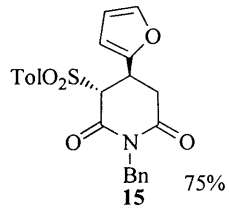
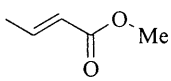
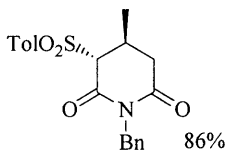
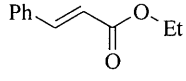
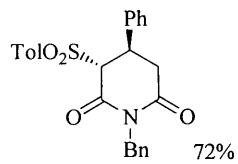
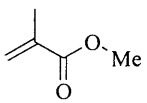
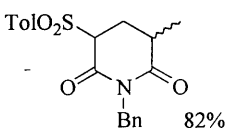
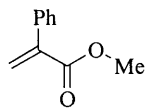
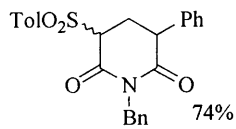
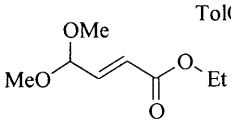
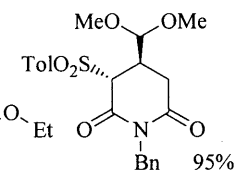
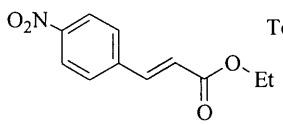
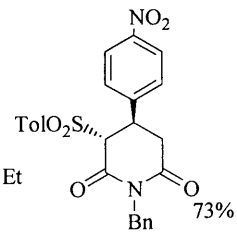
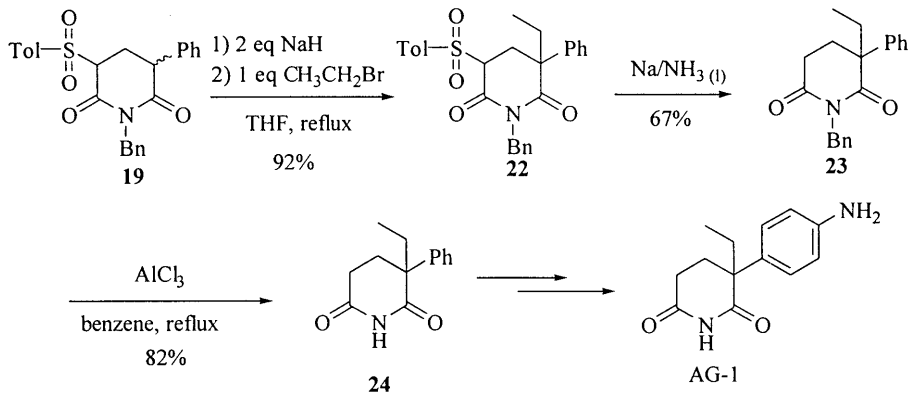
As summarized in Table 1, using this protocol, various 4- or 5-alkyl- or aryl-*N*-benzyl-3-toluenesulfonyl glutarimides were produced in moderate to excellent yields. More significantly, the presence of the sulfonyl group differentiates between $C_3$ and $C_5$ in **1** therefore allowing subsequent regioselective nucleophilic substitution. The carbonyl groups can be further elaborated making possible the introduction of different substituents at $C_2$ and $C_6$. We have successfully transformed **19** into **24**[4] (Scheme 2), which has been converted to AG-1,[3d] an efficient aromatase inhibitor and effective drug against breast cancer for postmenopausal patients.[5]

Table 1
[3+3] Reaction of dianion **4** with various Michael acceptors[a,b,c]

| Entry | Michael acceptor | Product | Entry | Michael acceptor | Product |
|---|---|---|---|---|---|
| 1 |  **6** |  90% **7** | 5 |  **14** |  75% **15** |
| 2 |  **8** |  86% **9** | 6 |  **16** |  72% **17** |
| 3 |  **10** |  82% **11** | 7 |  **18** |  74% **19** |
| 4 |  **12** |  95% **13** | 8 |  **20** |  73% **21** |

[a] All the yields were based on acetamide **3**.
[b] The structures of **9** and **13** were confirmed by X-ray analysis.
[c] For selected NMR spectral data for **7**, **15**, **19**, **22**, **23**, **24** see Ref. 6.

In conclusion, we have explored a formal [3+3] cycloaddition strategy that is synthetically useful for constructing 4- or 5-substituted-3-toluenesulfonylglutarimides. We are currently studying the scope of this process as well as additional applications of the methodology to the synthesis of piperidines, indolizidines, quinolizidines and indoles.




Scheme 2.

## Acknowledgements

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4. The $^{1}H$ and $^{13}C$ NMR spectra of **24**, in agreement with the literature,[3d] prove the regioselectivity of alkylation of **19**.
5. (a) Hartmann, R. W.; Batzl, C.; Pongratz, T. M.; Mannschreck, A. *J. Med. Chem.* **1992**, *35*, 2210 and references cited therein. (b) Harvey, H. A.; Lipton, A.; Santin, R. J. *Cancer Res. (suppl.)* **1982**, *42*, 3261.
6. Selected spectral data of **7**: $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.52 (d, $J=8.1$ Hz, 2H), 7.25–7.32 (m, 7H), 5.03 (d, $J=13.8$ Hz, 1H), 4.86 (d, $J=13.8$ Hz, 1H), 4.05–4.07 (m, 1H), 3.20–3.38 (m, 1H), 2.68–2.82 (m, 2H), 2.43 (s, 3H), 2.20–2.40 (m, 1H).
   Selected spectral data of **15**: $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.56 (d, $J=7.8$ Hz, 2H), 7.37 (d, $J=4.5$ Hz, 2H), 7.26–7.32 (m, 5H), 7.19 (s, 1H), 6.20 (s, 1H), 6.01 (d, $J=2.7$ Hz, 1H), 5.07 (d, $J=14.4$ Hz, 1H), 4.90 (d, $J=14.4$ Hz, 1H), 4.34–4.38 (m, 2H), 3.69 (dd, $J=6.3$, 18.0 Hz, 1H), 3.09 (d, $J=18.0$ Hz, 1H), 2.45 (s, 3H).
   Selected spectral data of **19**: $^{1}H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.86 (d, $J=8.1$ Hz, 4/9H), 7.55 (d, $J=8.4$ Hz, 14/9H), 7.11–7.39 (m, 12H), 5.07 (d, $J=13.8$ Hz, 1H), 4.95 (d, $J=13.8$ Hz, 1H), 4.90 (d, $J=2.7$ Hz, 2/9H), 4.51 (dd,

$J=5.7$, 12.3 Hz, 7/9H), 4.35 (dd, $J=5.7$, 12.3 Hz, 2/9H), 4.14 (dd, $J=3.3$, 5.7 Hz, 7/9H), 3.68 (dd, $J=3.3$, 5.7 Hz, 2/9H), 3.02 (ddd, $J=3.3$, 5.7, 15.0 Hz, 7/9H), 2.75–2.82 (m, 2/9H), 2.52–2.61 (m, 7/9H), 2.43 (s, 3H).

Selected spectral data of **22**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.79 (d, $J=8.5$ Hz, 2H), 7.32 (d, $J=8.5$ Hz, 2H), 7.21–7.26 (m, 8H), 6.93 (dd, $J=2.0$, 5.0 Hz, 2H), 4.97 (d, $J=13.5$ Hz, 1H), 4.88 (d, $J=13.5$ Hz, 1H), 4.04 (dd, $J=5.0$, 14.0 Hz, 1H), 3.05 (dd, $J=5.0$, 14.0 Hz, 1H), 2.59 (t, $J=14.0$ Hz, 1H), 2.44 (s, 3H), 2.06 (qd, $J=6.5$, 13.0 Hz, 1H), 1.91 (qd, $J=6.5$, 13.0 Hz, 1H), 0.86 (t, $J=6.5$ Hz, 3H).

Selected spectral data of **23**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.35 (d, $J=7.5$ Hz, 2H), 7.23–7.34 (m, 6H), 7.04 (d, $J=6.0$ Hz, 2H), 5.10 (d, $J=13.5$ Hz, 1H), 4.96 (d, $J=13.5$ Hz, 1H), 2.68 (d, $J=18.0$ Hz, 1H), 2.43–2.51 (m, 1H), 2.30–2.33 (m, 1H), 2.17–2.23 (m, 1H), 2.05 (qd, $J=6.0$, 12.0 Hz, 1H), 1.88 (qd, $J=6.0$, 12.0 Hz, 1H), 0.84 (t, $J=6.0$ Hz, 3H).

Selected spectral data of **24**: $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.85 (br s, 1H), 7.36–7.39 (m, 2H), 7.26–7.31 (m, 3H), 2.59 (dd, $J=4.0$, 13.5 Hz, 1H), 2.37–2.44 (m, 2H), 2.21–2.27 (m, 1H), 2.08 (qd, $J=7.5$, 15.0 Hz, 1H), 1.93 (qd, $J=7.5$, 15.0 Hz, 1H), 0.88 (t, $J=7.5$ Hz, 3H).