## Modified Julia–Kocienski Reaction Promoted by Means of *m*-NPT (Nitrophenyltetrazole) Sulfone

Yuki Sakai, Kazutada Ikeuchi, Yuji Yamada, Toshiyuki Wakimoto, Toshiyuki Kan\*

School of Pharmaceutical Sciences, University of Shizuoka and Global COE Program, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan Fax +81(54)2645745; E-mail: kant@u-shizuoka-ken.ac.jp

Received 1 December 2009

**Abstract:** *m*-Nitrophenyltetrazole sulfone (2) was employed in the Julia–Kocienski reaction. The olefination reaction between 2 and carbonyl compounds proceeded smoothly under Masamune–Roush conditions (DBU and LiCl). These conditions were also applicable to our catechin derivative synthesis. Furthermore, phenolic mesylate was also tolerated in this mild reaction.

Key words: olefination, Julia-Kocienski reaction, sulfone

Olefination reactions (Wittig, Peterson, and Julia reactions) are significant because of their applicability to the synthesis of natural products as well as pharmaceutical drugs.<sup>1</sup> In particular, the Horner–Wadsworth–Emmons reaction is attractive because the required carbanion can be generated under mild conditions such as treatment with LiCl and DBU.<sup>2</sup> Although many functional groups are compatible with the olefination reaction conditions, preparing the precursor phosphate derivatives by the Arbuzov reaction requires harsh conditions. Recently, the Julia-Kocienski reaction (J-K reaction)<sup>3</sup> has attracted much attention because the phenytetrazole sulfone (PTsulfone) group can be prepared under mild conditions (Scheme 1). However, the generation of the anion of 1 requires a strong base at low temperature (LHMDS, -78 °C). During the course of our investigations into the synthesis of nitrogen-containing natural products, we found that the nitrobenzenesulfonamide anion plays a key role in the excellent performance of a number of intermolecular as well as intramolecular reactions.<sup>4–7</sup> Inspired by this finding, we have investigated the synthesis of nitro-PT-sulfone 2, which should generate the anion under mild conditions. Herein, we report the synthesis of nitro-PTsulfone 2 and on its application in the J-K reaction.



Scheme 1 The Julia-Kocienski reaction and its modification

As shown in Scheme 2, nitrophenyltetrazolethiols **5** and **6** were prepared according to Aïssa's protocol.<sup>8</sup> Treatment of aniline derivatives **3** and **4** with  $CSCl_2$  gave the corre-

SYNLETT 2010, No. 5, pp 0827–0829 Advanced online publication: 10.02.2010 DOI: 10.1055/s-0029-1219386; Art ID: U11409ST © Georg Thieme Verlag Stuttgart · New York sponding thioisocyanate; subsequent cycloaddition reaction with sodium azide provided the tetrazole derivative as a mixture of tautomers. Finally, treatment with  $Et_3N$ , and conversion from the thione into the corresponding thiol proceeded smoothly to give desired products **5** and **6** (from **3** and **4**, respectively).



Scheme 2 Syntheses of nitrophenyltetrazolethiols 5 and 6

Initially, we focused on *p*-nitro-PT-sulfone **8**, which should be more active than the corresponding *m*-nitrophenyl derivatives. PT-sulfone **8** was prepared by condensation of alkyl halides **7** with **5** under basic conditions and subsequent oxidation with *m*-CPBA (Scheme 3). As shown in Table 1, several basic conditions were tested for the condensation with benzaldehyde (**9**). Although the reaction proceeded, satisfactory results were not obtained even in the presence of a mild base such as  $Cs_2CO_3$  or DBU. Furthermore, the decomposition product<sup>9</sup> was observed under all the basic conditions; thus, we focused on *m*-nitrophenyltetrazolesulfone (*m*-NPT sulfone) derivative **12**.



Scheme 3 Synthesis of *p*-NPT sulfone 8 and olefination to 10

```
Table 1Coupling of 8 and 9
```

| Entry | Conditions                                   | Yield (%) | $E/Z^{\rm a}$ |
|-------|--|-----------|---------------|
| 1     | LHMDS, THF, –78 °C                           | 46        | 19:1          |
| 2     | Cs <sub>2</sub> CO <sub>3</sub> , MeCN, r.t. | 37        | 10:1          |
| 3     | DBU, MeCN, 0 °C                              | trace     | 5:1           |
| 4     | DBU, LiCl, MeCN, 0 °C                        | 28        | 9:1           |

<sup>a</sup> Determined by <sup>1</sup>H NMR.

As shown in Scheme 4, *m*-NPT sulfone 12 was prepared from 11 and 6 in a manner similar to that for 8. Table 2 summarizes the results of the coupling reaction with 9. With this reagent, the reaction proceeded in the presence of either  $Cs_2CO_3$  or DBU at room temperature (entries 2 and 3). Because decomposition products were not observed in the reaction with DBU, further modifications were tested (Table 2). We found that the addition of LiCl to DBU (entry 4) increased the yield significantly. To our knowledge, this is the first example of the J–K reaction performed under such mild conditions.



Scheme 4 Synthesis of *m*-NPT sulfone 12 and olefination with 9

Table 2 Coupling of 12 and 9

| Entry | Conditions                                   | Yield (%) | $E/Z^{\rm a}$ |
|-------|--|-----------|---------------|
| 1     | LHMDS, THF, –78 °C                           | 76        | 23:1          |
| 2     | Cs <sub>2</sub> CO <sub>3</sub> , MeCN, 0 °C | 41        | 9:1           |
| 3     | DBU, MeCN, 0 °C                              | 50        | 10:1          |
| 4     | DBU, LiCl, MeCN, 0 °C                        | 86        | 7:1           |
| 5     | DBU, NaI, MeCN, 0 °C                         | 77        | 27:1          |
|       |  |           |               |

<sup>a</sup> Determined by <sup>1</sup>H NMR.

Further applications of the modified J–K reaction were demonstrated in the synthesis of an intermediate for use in the synthesis of catechin (Scheme 5).<sup>10</sup> PT-sulfone **14** was prepared by a condensation reaction of **13** and **6**, with subsequent oxidation by *m*-CPBA.<sup>11</sup> Upon treatment of **14** and **15** with LiCl and DBU, the *E*-selective olefination reaction proceeded smoothly to provide **16**.<sup>12</sup>



Scheme 5 Synthesis of catechin derivative intermediate 16



Scheme 6 Comparison of reaction conditions

Furthermore, one advantage of the modified J–K reaction conditions in comparison with the usual conditions is demonstrated in Scheme 6. Because hydrolysis of phenolic mesylate readily occurs upon exposure to LHMDS,<sup>13</sup> a coupling reaction of **17** and **18** under the usual conditions resulted in low yield. In contrast, the coupling reaction between **14** and **18**, in the presence of a combination of LiCl and DBU, proceeded smoothly to provide **19** in high yield.

In conclusion, we have successfully developed an efficient Julia–Kocienski reaction mediated by *m*-NPT sulfone. Considering the mild reaction conditions, this reaction should proceed in the presence of a wide range of functional groups. Further applications of this method are currently underway in our laboratory.

## Acknowledgment

This work was financially supported by Takeda Science Foundation, Naito Foundation, Nagase Science, and a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

## **References and Notes**

- (1) Aïssa, C. Eur. J. Org. Chem. 2009, 12, 1831.
- (2) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
- (3) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. Synlett 1998, 26.
- (4) Kan, T.; Fukuyama, T. Chem. Commun. 2004, 353.
- (5) For the use of nitro-substituted aromatic rings for selenation, see: Grieco, P. A.; Gilman, S.; Nishizawa, M. J. Org. Chem. 1976, 41, 1485.
- (6) For azidation, see: Mizuno, M.; Shioiri, T. Chem. Commun. 1997, 2165.
- (7) For macrolactonization, see: (a) Shiina, I.; Ibuka, R.;
  Kubota, M. *Chem. Lett.* 2002, 286. (b) Shiina, I. *Chem. Rev.* 2007, *107*, 239.
- (8) Aïssa, C. J. Org. Chem. 2006, 71, 360.
- (9) Upon treatment of similar *p*-NPT sulfone derivative 20, under basic conditions, the self-condensation reaction proceeded through Meisenheimer complex 21 to provide 22, as shown in Scheme 7.



Scheme 7 Decomposition of 20 under basic conditions

- (10) Hirooka, Y.; Nitta, M.; Furuta, T.; Kan, T. Synlett **2008**, 3234.
- (11) Synthesis of sulfone **14**: To a stirred solution of iodide **13** (26 mg, 70  $\mu$ mol) and *m*-NPTSH **6** (25 mg, 110  $\mu$ mol) in DMF (1.0 mL), was added K<sub>2</sub>CO<sub>3</sub> (15 mg, 110  $\mu$ mol) at room temperature. After stirring for 90 min, the reaction mixture was quenched with sat. aq NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with sat. aq NH<sub>4</sub>Cl and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue (28 mg) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was treated with *m*-CPBA (42 mg, 244 mmol) and, after stirring at 40 °C for 10 h, the reaction mixture was quenched with sat. aq Na<sub>2</sub>SO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with sat. aq Na<sub>2</sub>SO<sub>3</sub> and sat. aq NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by preparative TLC to yield sulfone **14** (21 mg, 43 mmol, 62%, 2 steps). Spectral data for **14**: IR

- (neat): 837, 1101, 1157, 1352, 1539, 2929 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 0.28$  (s, 6 H), 1.01 (s, 9 H), 3.27 (t, J = 8.2 Hz, 2 H), 4.07 (t, J = 8.2 Hz, 2 H), 6.83 (d, J = 8.0Hz, 1 H), 6.91 (t, J = 8.0 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.20 (d, J = 8.0 Hz, 1 H), 7.84 (t, J = 8.5 Hz, 1 H), 8,09 (dt, J = 8.5, 1.0 Hz, 1 H), 8.51 (dt, J = 8.5, 1.0 Hz, 1 H), 8.61 (t, J = 1.0 Hz, 1 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = -4.0$ , 18.3, 24.4, 25.9, 55.7, 118.7, 120.8, 121.5, 126.2, 126.4, 128.9, 130.8, 130.9, 131.0, 133.9, 148.7, 153.7, 154.0; FAB-MS: m/z = 490 [M + H]<sup>+</sup>; HRMS: m/z [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>28</sub>O<sub>3</sub>N<sub>5</sub>SSi: 490.1580; found: 490.1595.
- (12) Synthesis of 16: To a stirred solution of sulfone 14 (11 mg, 22  $\mu$ mol), aldehyde 15 (13 mg, 26  $\mu$ mol) and LiCl (4.0 mg, 78 µmol) in MeCN (1.0 mL) at 0 °C, DBU (12 µL, 78 µmol) was added dropwise. After stirring for 20 min, the reaction mixture was quenched with sat. aq NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with sat. aq NH<sub>4</sub>Cl and brine, dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by preparative TLC to yield 16 (11 mg, 18 µmol, 81%). Spectral data for 16: IR (neat): 839, 1116, 1573, 1693, 2927 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 0.25 (s, 6 H), 1.02 (s, 9 H), 3.50 (d, J = 7.3 Hz, 2 H), 5,04$ (s, 2 H), 5.08 (s, 4 H), 6.25–6.27 (m, 2 H), 6.65 (d, J = 11.6 Hz, 1 H), 6.82 (s, 2 H), 6.91 (d, J = 8.5 Hz, 1 H), 7.10–7.43 (m, 17 H); <sup>13</sup>C NMR (68 MHz, CDCl<sub>3</sub>):  $\delta$  = -4.1, 18.3, 25.8, 33.6, 71.1, 71.2, 75.3, 105.9, 118.4, 121.1, 127.2, 127.3, 127.4, 127.7, 127.8, 128.1, 128.4, 128.5, 128.6, 130.3, 130.5, 130.7, 133.5, 137.2, 137.8, 137.9, 152.9, 153.4; FAB-MS:  $m/z = 642 [M]^+$ ; HRMS:  $m/z [M]^+$  calcd for  $C_{42}H_{46}O_4Si$ : 642.3165; found: 642.3162.
- (13) (a) Kita, Y.; Toma, T.; Kan, T.; Fukuyama, T. Org. Lett. **2008**, 10, 3251. (b) For a similar deprotection of the Ms group by LDA, see: Ritter, T.; Stanek, K.; Larrosa, I.; Carreira, E. M. Org. Lett. **2004**, *6*, 1513.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.