COMMUNICATION

Facile synthesis of disubstituted and spiro five-membered benzosultams mediated by TMSCl–NaI–MeCN reagent

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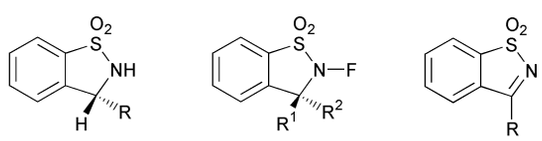
***o*-Lithiation of *N-tert*-butylbenzenesulfonamide followed by reaction with ketones gave carbinol sulfonamides, which underwent TMSCl–NaI–MeCN reagent mediated cyclization to afford 3,3-disubstituted and spiro-2,3-dihydrobenzo[*d*]isothiazole-1,1-diones in high yields.**

Oppolzer's saccharine derived benzosultams **1**, **2**[1,2] are an important class of chiral auxiliaries that have many applications in asymmetric reactions such as alkylation,[1c] acylation,[1c] aldolization,[1c] Diels–Alder reactions[1b,d] and azidation.[2b] However, the existence of acidic benzyl protons in **1**, and **2** sometimes makes them unsuitable as templates for enantioselective fluorinating reagents,[3] see for example ref. 3*f*. As a part of our continuing studies on the development of novel fluorinating reagents **3** based on sultam templates,[3e–3i] we are interested in 3,3-disubstituted 5-membered benzosultams and spirobenzosultams. These sultams have also received attention as potent HIV-1 inhibitors.[4]



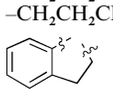
1: R=Me
2: R=Bu^t

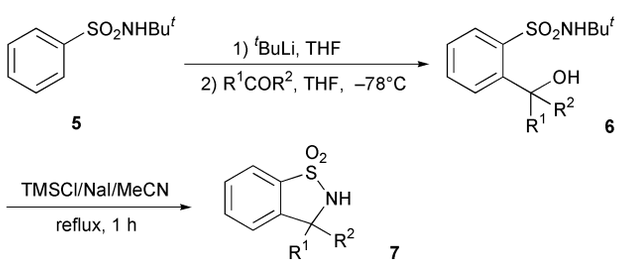
3 **4**

3,3-Disubstituted 2,3-dihydrobenzo[*d*]isothiazole-1,1-diones are usually prepared by addition of organolithium compounds or Grignard reagents to the *N*-sulfonylimine **4**.[1b,d,2a,3e,5,6] However, these methods have limitations owning to the unavailability or poor reactivity of some hindered organometallic species. In fact, only a limited number of such compounds have been prepared in this way. Watanabe *et al.* have reported cyclization methods for the preparation of *N*-methyl or phenyl 3,3-disubstituted five-membered benzosultams under acidic or thermal conditions,[7a] however, the difficulty in removing the methyl or phenyl protective group made the method impossible for general use. Moreover, there are no reported methods for the synthesis of spiro-2,3-dihydrobenzo[*d*]isothiazole-1,1-diones. Recently we have developed a novel cyclization mediated by TMSCl–NaI–MeCN reagent for the construction of 3,3-disubstituted and spiro six-membered benzosultams.[3g] In this paper, we show a new method for the facile preparation of 3,3-disubstituted and spiro-2,3-dihydrobenzo[*d*]isothiazole-1,1-diones (Scheme 1).

ortho-Lithiation of *N*-substituted benzenesulfonamides is a well established method for the preparation of their *o*-functionalized derivatives and heterocycles.[6,7] We first attempted the *ortho*-lithiation using *N*-Boc-benzenesulfonamide. *N*-Boc-benzenesulfonamide was treated with excess *tert*-BuLi (2.5 equiv.) followed by the addition of 1.1 equivalent of anhydrous acetone, however, there was no expected carbinol sulfonamide formed, only the removal of the Boc protecting group was observed which yielded benzenesulfonamide. *N-tert*-Butylbenzenesulfonamide (**5**) was next used for the reaction. The

Table 1 Synthesis of 3,3-disubstituted and spiro-five-membered benzosultams

Entry	R^1	R^2	Yields (%) **6a–g**	Yields (%) **7a–g**
a	Me	Me	85	95
b	Me	Ph	86	99
c	Me	4-Methylphenyl	84	92
d	Me	1-Naphthyl	55	98
e		$-CH_2CH_2CH_2CH_2-$	76	96
f		$-CH_2CH_2CH_2CH_2CH_2-$	70	92
g			83	96



Scheme 1

ortho-lithiation of **5** proceeded smoothly to furnish an anion, which reacted with acetone to give the carbinol sulfonamide **6a** in 85%, isolated yield (Table 1, entry a). The sulfonamide **6a** was subjected to TMSCl–NaI–MeCN reagent (2 equiv.) under refluxing conditions to form benzosultam **7a** in 95% yield.[8] The sultam **7a** is a known template for a fluorinating reagent.[9] To examine the scope and generality of this method, we examined the reactions using various ketones ranging from alkyl and aryl ketones to cyclic ketones. In all cases, the corresponding carbinol sulfonamides **6** were obtained in good yields, and the sultams **7** including spiro sultams **7e–g** were formed nearly quantitatively (Table 1). This method provided a general synthesis of 3,3-disubstituted five-membered benzosultams **7**. As far as we know, this is the first example of a synthesis of spiro-2,3-dihydrobenzo[*d*]isothiazole-1,1-diones.

The 3D structure of spirosultam **7g** would be interesting, since the two flat benzo[*d*]isothiazole and indan rings in **7g** are orthogonalized on the spiro carbon. We finally obtained the optically pure **7g** to form a new chiral auxiliary. Racemic **7g** was treated with NaH (2 equiv.) in THF and it was reacted with (+)-10-camphorsulfonyl chloride (1.5 equiv.) overnight to form two diastereomers, the less polar (+)-**8** and the more polar (−)-**8**, in 22% and 24% isolated yields, respectively. The unreacted racemic **7g** was recovered (44%). Removing the chiral auxiliary of (+)-**8** and (−)-**8** under Oppolzer's conditions (conc. H_2SO_4),[1d] to our surprise, gave racemic **7g**.[10] However, when aq. LiOH (2 M) was used for the hydrolysis, the reaction went slowly at room temperature to furnish the optically pure (−)-**7g**[11] and (+)-**7g**[11] in high yields without racemization.

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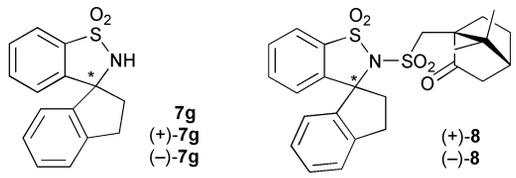

In summary, we have developed a facile synthesis of 3,3-disubstituted and spiro-2,3-dihydrobenzo[*d*]isothiazole-1,1-diones mediated by the TMSCl–NaI–MeCN reagent. It is worth noting that spiro five-membered benzosultams such as **7e**–**g** were obtained for the first time. Optically pure benzosultams (+)-**7g** and (−)-**7g** would be useful as chiral auxiliaries for asymmetric synthesis. Considering the diverse biological profiles of sulfonamide derivatives, these benzosultams may also be used for biological evaluations and as possible substrates for developing sulfonamide peptidomimetics.[12]

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8 Typical experimental procedure: **A**. To a stirred solution of *N*-*tert*-butylbenzenesulfonamide (1.07 g, 5 mmol) in THF (25 mL) was added a 1.50 M solution of *tert*-BuLi in hexane (10 mL, 15 mmol) under nitrogen at −78 °C. The reaction mixture was stirred for 15 min at −78 °C, warmed to 0 °C, stirred for an additional 1 h, and cooled to −78 °C. A solution of anhydrous acetone (0.29 g, 5 mmol) in THF (5 mL) was added. After 2 h, saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc, the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (30% EtOAc in hexane) to give the carbinol sulfonamide **6a** (1.15 g, 85%) as colorless prisms: mp 124–126 °C; IR (KBr) 3460, 3241 cm^{-1}; ^1H NMR δ 1.24 (s, 9H), 1.68 (s, 6H), 4.45 (s, 1H), 6.24 (s, 1H), 7.30–7.36 (m, 2H), 7.45–7.51 (m, 1H), 8.18 (m, 1H); ^{13}C NMR δ 30.7, 33.3, 55.4, 74.9, 127.0, 129.3, 129.8, 132.0, 140.4, 147.2; MS *m*/*z* 271 (M^+), 256 (M^+ − Me). Anal. Calcd for $C_{13}H_{21}NO_3S$: C, 57.54; H, 7.80; N, 5.16. Found: C, 57.59; H, 7.75; N, 5.06%. **B**. To a stirred solution of **6a** (0.55 g, 2 mmol) in MeCN (10 mL) was added under nitrogen, sodium iodide (0.60 g, 4 mmol) and chlorotrimethylsilane (0.51 mL, 4 mmol). The reaction mixture was refluxed for 1 h. It was cooled to room temperature and 10% sodium thiosulfate aqueous solution was added. The mixture was extracted with EtOAc, and the combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (30% EtOAc in hexane) to give sultam **7a** (0.37 g, 95%) as colorless prisms.

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10 It was determined by analytical HPLC method using Chiralcel AD column (hexane–*i*-PrOH–CF_3COOH = 80 : 20 : 0.1; flow rate: 0.5 ml min^{-1}). Two peaks of about the same size appeared at 23 and 28 minutes. This is in agreement with the results of racemic **7g** analyzed by the same method.

11 (−)-**7g**: $[\alpha]_D^{27}$ −6.4 (*c* 0.75, $CHCl_3$); IR (KBr) 3235 cm^{-1}; ^1H NMR δ 2.53 (dt, *J* = 13.4, 8.0 Hz, 1H), 3.12 (ddd, *J* = 16.4, 8.3, 3.6 Hz, 1H), 3.27 (dt, *J* = 16.1, 7.8 Hz, 1H), 4.65 (s, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.15 (m, 1H), 7.22 (m, 1H), 7.35 (m, 2H), 7.52–7.61 (m, 2H), 7.81–7.84 (m, 1H); ^{13}C NMR δ 30.7, 42.5, 73.5, 121.0, 123.8, 124.4, 125.3, 127.9, 129.4, 129.7, 133.6, 136.1, 143.5, 144.4; MS *m*/*z* 271 (M^+); HRMS calcd for $C_{15}H_{13}NO_2S$: 271.0667, found 271.0658. Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.22; H, 4.80; N, 5.08%. (+)-**7g**: $[\alpha]_D^{27}$ +6.7 (*c* 1.12, $CHCl_3$).

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