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A 1,5-benzothiazepine synthesis

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ABSTRACT

The pharmaceutically active compound (±)-thiazesim was synthesized in four steps and 62% overall yield. This new approach to biologically relevant benzothiazepine ring systems features the use of water as a solvent, co-solvent or catalyst in three of the four steps.

Benzothiazepines constitute valuable structural units in the field of pharmaceutical research.[1,2] In particular, incorporation of the 1,5-benzothiazepine unit has resulted in compounds with attractive biological profiles.[3] Some successfully marketed 1,5-benzothiazepines are shown in Figure 1 and include the multi-billion dollar-a-year selling antipsychotic quetiapine (**1**) (tradename Seroquel®),[4–7] the angina relieving calcium channel blocker diltiazem (**2**)[8–11] and the antihypertensive agent clentiazem (**3**).[12–14] Such a wealth of biological activities has provided impetus for chemists to invent a number of synthetic strategies to access the 1,5-benzothiazepine scaffold.[1,2]

A major challenge facing the pharmaceutical industry is the development of sustainable manufacturing processes that deliver target compounds in an energy efficient and ecologically benign manner.[15–17] In this regard, the use of water-tolerant chemistry has become increasingly important.[18–20] We have recently reported the energy efficient and operationally simply 'on-water'[21] addition of anilines to *N*-acryloyl-2,5-dimethylpyrrole.[22] During that work, we noted that thiophenols were excellent substrates for the reaction. In a competitive conjugate addition reaction, we anticipated that the thiophenol would exert its greater nucleophilicity and participate in the exclusion of aniline (Scheme 1). As such, we projected that the reaction of *ortho*-aminothiophenol (**5**) with a suitable α,β-unsaturated-*N*-acylpyrrole **6** would proceed via initial conjugate addition of the thiol, leaving the amine available for a trans-amidation reaction with the *N*-acylpyrrole unit to produce a benzothiazepinone ring **7**. While our earlier work focused on terminal α,β-unsaturated-*N*-acylpyrroles, the current strategy required an extension of that methodology to include substituted alkenes such as **6**, necessary for access to important pharmaceutical compounds. This Letter details the results of our initial foray into the synthesis of 1,5-benzothiazepines.

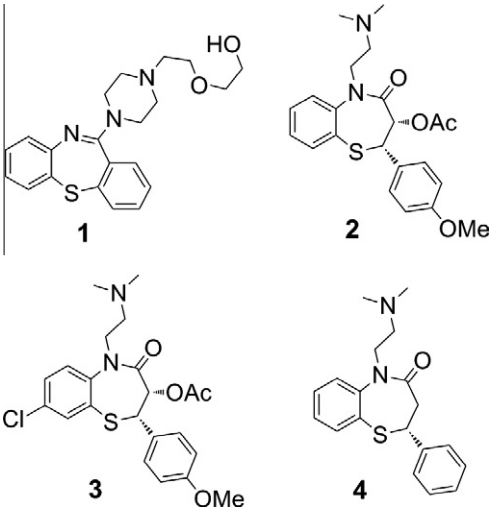

Figure 1. Examples of 1,5-benzothiazepines.

As an initial target on which to focus our efforts, we were drawn to the $GABBA_A$ blocker,[23] thiazesim (**4**) (Fig. 1). This relatively simple 1,5-benzothiazepine-containing compound was one of the first members of the class to be identified as an anti-depressant,[24,25] and was marketed as the hydrochloride salt (tradename, Altinil). As detailed retrosynthetically in Scheme 2, we envisaged that

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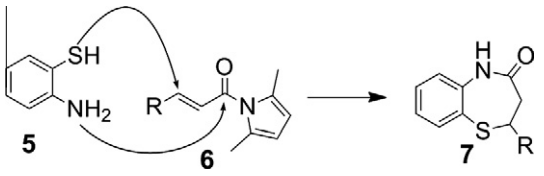
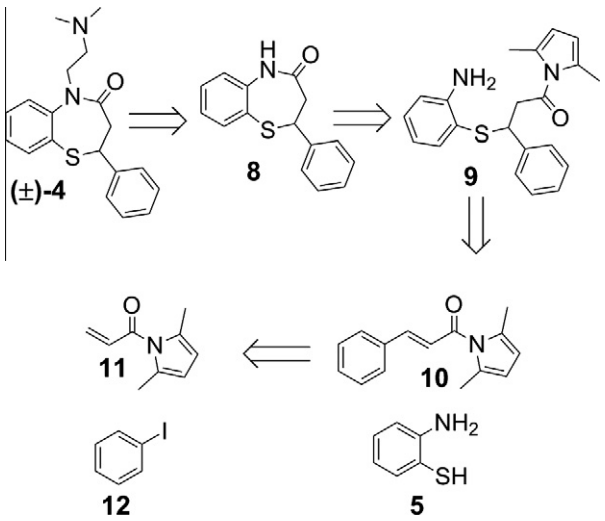


Scheme 1. Competitive conjugate addition.

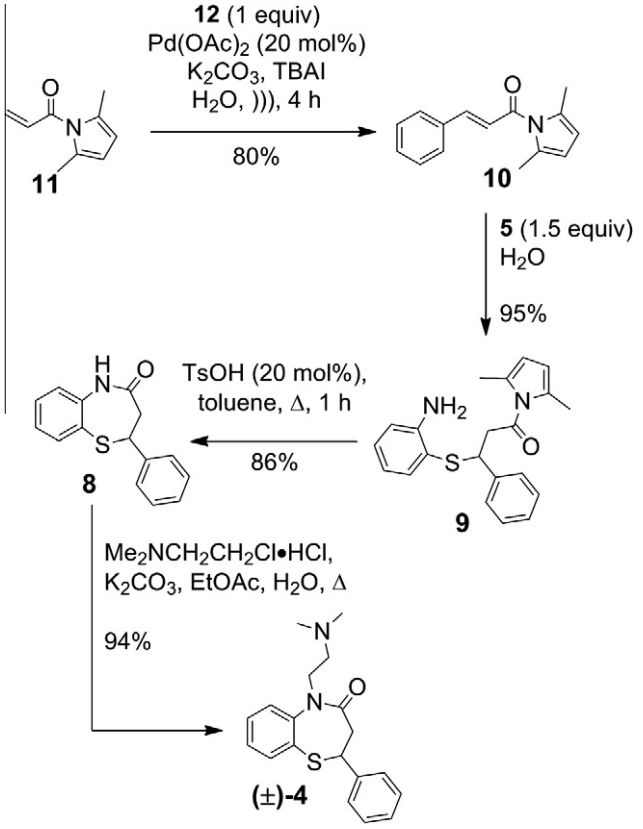
N-alkylation of the 1,5-benzothiazepinone core **8** would provide thiazesim in a straightforward manner. Disconnection of the amide C–N bond in **8** revealed **9**, containing both an aniline and an *N*-acyl-2,5-dimethylpyrrole activated acid equivalent. Disconnection of the C–S bond suggested an on-water conjugate addition of *ortho*-aminothiophenol (**5**) to the *N*-cinnamoyl-2,5-dimethylpyrrole **10**. In keeping with our current research focus,[22,26] compound **10** was envisaged to arise via an aqueous Heck reaction between alkene **11** and iodobenzene (**12**).

It is pertinent to note that we targeted the synthesis of (±)-thiazesim. In contrast to the recently reported application of a chiral Brønsted acid in aqueous media[27]—where formation of a close-ion pair allowed the chiral counterion to exert an influence over the stereochemical course of a reaction—the acid-catalysis responsible for on-water rate accelerations[26] can only deliver the conjugate addition product **9** in a racemic fashion. However, we did not view this as a major drawback. As long ago as 1927, it was recognised that benzothiazepinones could be resolved with an appropriate reagent.[28] Since 1968, such resolution techniques have been applied to the commercial synthesis of benzothiazepines.[25,29] Given the resolvability of the enantiomers, we felt that the inherent gains of such an operationally simple and relatively energy-frugal synthetic route counter-balanced the need for a resolution step.

The racemic synthesis began with the efficient Heck coupling of iodobenzene (**12**) and *N*-acryloyl-2,5-dimethylpyrrole (**11**) under the aqueous conditions reported by Wang, Zhou and co-workers,[30] (Scheme 3). The *E*-configured *N*-cinnamoyl-2,5-dimethylpyrrole (**10**) was the sole product and was formed in high yield. Since iodobenzene (**12**) is more dense than water and the *N*-acryloyl-2,5-dimethylpyrrole (**11**) is less dense than water, the conditions reported employed a phase-transfer agent and the use of sonication to ensure that the two reactants came into contact. We were intrigued by the possibility that emulsion formation would also serve as a method to facilitate the reaction. We were encouraged by reports of Heck couplings occurring at both room temperature and



Scheme 2. Retrosynthetic analysis.



Scheme 3. Synthesis of (±)-thiazesim **4**.

elevated temperature in neat water.[31,32] In the event, vigorously stirring a mixture of **11** and **12** in water at ambient temperature for 6 h delivered the desired product **10** in 14% yield. Increasing the temperature to 50 °C with vigorous stirring gave the coupled product **10** in 28% yield. Extending the reaction time to 24 h at room temperature provided **10** in 50% yield. Whilst providing successful access to **10** and being more energy efficient, this protocol was not as satisfactory as the initial procedure in terms of yield.

Compound **10** was then reacted with *ortho*-aminothiophenol (**5**) 'on-water',[21] (Scheme 3). This delivered the coupled product in high yield. We had hoped that the aniline unit would be nucleophilic enough to undergo a spontaneous cascade lactamisation with the acylpyrrole unit and provide **8** directly, but this proved not to be the case. Attempts to encourage the lactamisation with basic reagents such as DMAP or triethylamine led exclusively to elimination of the β-thiophenol. This is not surprising given that the carbonyl unit of *N*-acylpyrroles is more ketone-like than amide-like, and the acidity of the α-hydrogens is accordingly affected.[33] To circumvent this unwanted elimination reaction, an acid-catalysed ring-closure was dictated. Since the lactamisation reaction did not spontaneously occur under the 'on-water' conditions used for effecting the conjugate addition, we concluded that the interfacial water at the surface of the emulsion droplets was not acidic enough to effect the desired transformation. Beattie and co-workers have measured the isoelectric point of oil-in-water emulsions to be between pH 3 and 4, suggesting a pK_a of approximately 7 for the interfacial water molecules.[34,35] We therefore elected to employ a much stronger acid to effect the transformation. Reaction of compound **9** with HCl in acetone returned a complex mixture that did not contain the desired product. Treating compound **9** with *para*-toluenesulfonic acid in THF delivered the desired benzothiazepinone **8** in moderate yield (22%) accompanied by unreacted starting material. Increasing the reaction tempera-

ture by microwave irradiation of the THF solution, gave the desired compound **8** in trace amounts only. We reasoned that the difference in product distribution between the two solvents (acetone and THF) reflected their ability to stabilise the reactive conformation of the precursor **9**. As the precursor **9** contains three aromatic rings, we expected that employing an aromatic solvent may prove useful. In the event, we were pleased to observe that treatment of **9** with *para*-toluenesulfonic acid in toluene delivered the desired benzothiazepinone **8** in high yield (86%) in just 1 h. Although the ring-closure required heating, the short reaction time represented an improvement to the harsh conditions previously used to close analogous seven-membered rings.[1,2] To complete the synthesis, compound **8** was N-alkylated with (2-chloroethyl)dimethylamine in wet ethyl acetate to give (±)-thiazesim **4** in excellent yield.

In summary, we have completed a four step synthesis of the pharmaceutically active compound (±)-thiazesim **4**, in 62% overall yield. This work illustrates a new synthetic approach to biologically relevant benzothiazepine ring systems. In keeping with the need to develop water tolerant routes to pharmaceuticals, water featured as a solvent, co-solvent or catalyst in three of the four steps. We are currently exploring the scope of this new protocol with the aim of rapidly accessing a library of benzothiazepine analogues. The outcomes of that work will be reported in due course.

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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.2011.01.098.

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