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Silver nitrate-promoted ring enlargement of 1-tribromomethyl-1,2-dihydro- and 1-tribromomethyl-1,2,3,4-tetrahydro-isoquinoline derivatives: application to the synthesis of the anti-anginal zatebradine

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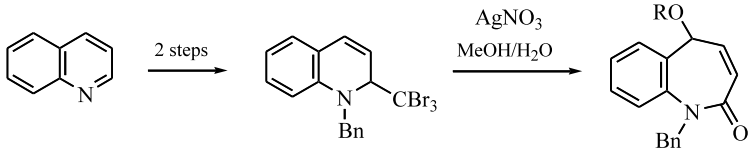
Abstract—The one step $AgNO_3$-mediated ring enlargement of 1-tribromomethyl-1,2-dihydro- and 1-tribromomethyl-1,2,3,4-tetrahydro-isoquinoline derivatives into 1,2-dihydro- and 1,2,3,4-tetrahydro-benzo[*d*]azepin-2-ones, respectively, is reported. This reaction offers a convenient entry to potentially active substances such as the anti-anginal zatebradine.

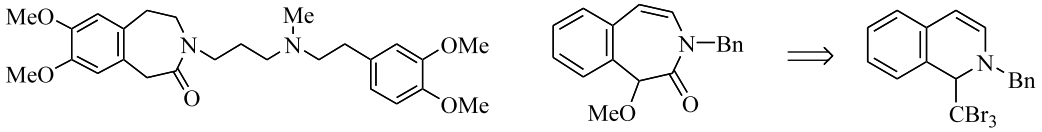
We have recently disclosed[1] a new ring enlargement process that allows the one-step transformation of the 1-benzyl-2-tribromomethyl-1,2-dihydro-quinoline **1** into the 1,5-dihydro-benzo[*b*]azepin-2-one **2a** under the influence of silver nitrate in a hydromethanolic medium (Scheme 1).

Such a structural transformation would be of higher value if it could be applied to other heterocycles embodying the generic motif $R_1R_2N\text{-}CH(R_3)\text{-}CBr_3$. For instance, the formation of the dihydro-benzo[*d*]azepin-3-one **4a** could be expected by applying the conditions of the rearrangement shown in Scheme 1 to the 2-benzyl-1-tribromomethyl-1,2-dihydro-isoquinoline **5** (Scheme 2). It is worthy of note that dihydro- and tetrahydro-benzo[*d*]azepin-2-one rings are found as constituents of natural products and of medicinally important compounds such as the anti-anginal zatebradine **3**.[2] Herein, we report the feasibility of such an approach to reach the 1,3-dihydro-benzo[*d*]azepin-2-



Quinoline **1** **2** **a** : R = Me **b** : R = H

Scheme 1.



Zatebradine **3** **4a** **5**

Scheme 2.

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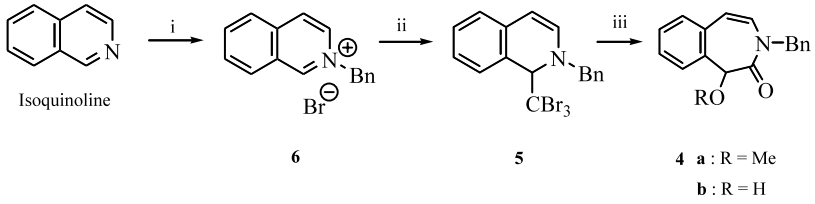
one **4a** and also illustrate further its synthetic potential by the realisation of a new synthesis of zatebradine **3**.

The key 2-benzyl-1-tribromomethyl-1,2-dihydro-isoquinoline **5** was prepared in two high yielding steps from isoquinoline as reported in Scheme 3. Subjected to the action of an excess of silver nitrate in $MeOH/H_2O$ (10:1), **5** rearranged into the expected dihydro-benzo-[*d*]azepin-2-one **4a**[3] which was isolated in 44% yield (Scheme 3).

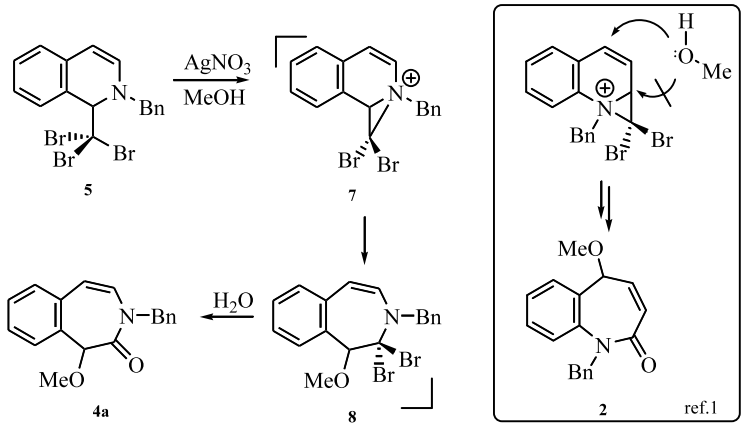
The formation of **4a** may be accounted for by assuming (Scheme 4): (1) the transient formation of an aziridinium ring (intermediate **7**) under the electrophilic assistance of a silver ion; (2) methanol opening of the aziridinium ring; (3) subsequent hydrolysis of the resulting α,α-dibromo amine moiety in the intermediate **8**. It is worthy of note that, in the absence of any other mechanistic possibility and contrary to what happened in the quinoline series[1] (Scheme 4, cartouche), the opening of the transient aziridinium ring in **7** takes place by nucleophilic attack at its benzylic carbon.

With the precedent result in hand we next turned our attention to the synthesis of zatebradine **3**, a drug which has attracted biologists's interest over the years because of its anti-anginal properties. Scheme 5 shows the key bond disconnections in our retrosynthetic analysis.

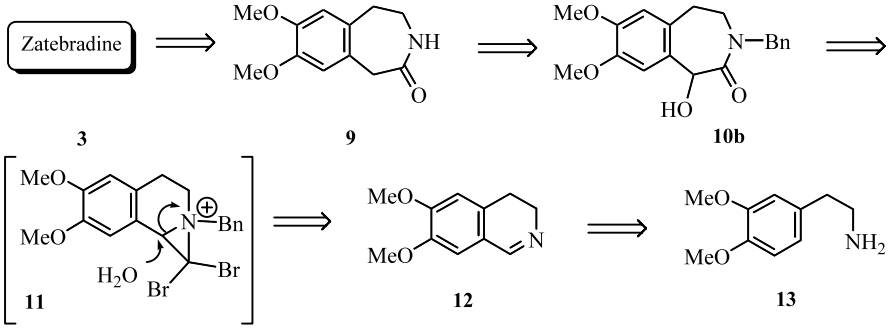
Although the 6,7-dimethoxy-isoquinoline could have been considered as a valuable intermediate for the synthesis of zatebradine, it appears to us that the total number of steps to reach the advanced intermediate **10** could be reduced if: (1) the 6,7-dimethoxy-3,4-dihydro-isoquinoline **12**, easily prepared from the commercially available 2-(3,4-dimethoxy-phenyl)-ethylamine **13**,[4] could be used as substrate for the key ring enlargement reaction, and if (2) the transient aziridinium species **11** could be trapped by water, instead of methanol.



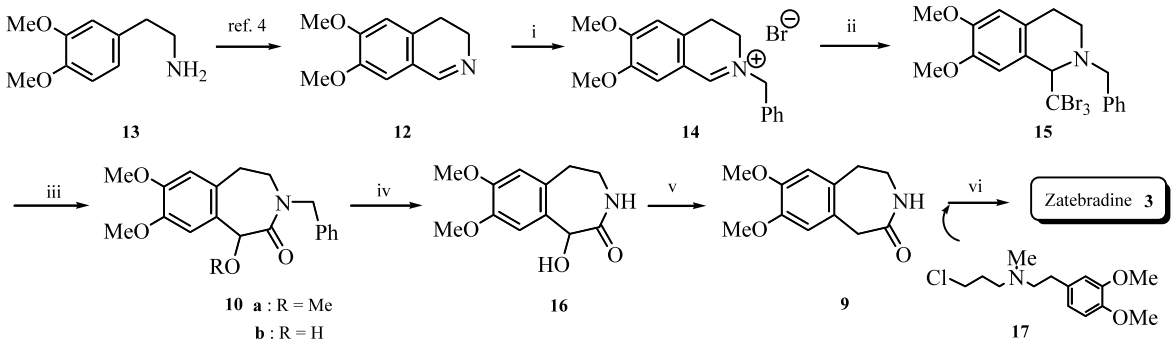
Scheme 3. *Reagents and conditions*: (i) $PhCH_2Br$ (1.1 equiv.), MeOH, reflux for 2 weeks (quant.); (ii) **6** dissolved in CH_3CN/H_2O (1/1) then $HCBr_3$ (1.3 equiv.) and aq. KOH (1.2 equiv.), rt, 45 min (89%); (iii) **5** in MeOH at −40°C then aq. $AgNO_3$ (3 equiv.), up to rt, 16 h (44%).



Scheme 4.



Scheme 5.



Scheme 6. *Reagents and conditions*: (i) $PhCH_2Br$ (2 equiv.), tol, reflux, 2 h (89%), (ii) **14** dissolved in CH_3CN/H_2O (1/1) then $CHBr_3$ (1.2 equiv.) and aq KOH (1.1 equiv.), rt, 3 h (76%; white solid, mp: 106–108°C); (iii) see Ref. 7; (iv) Na, liq. NH_3, THF, −78°C, 30 min (95%; white solid, mp: 180–182°C); (v) Me_3SiCl (6 equiv.), NaI (6 equiv.), CH_3CN, rt, 24 h (98%; white solid, mp: 186–188°C); (vi) *t*BuOK, DMSO, 50°C, 2 h (40%).

Following these considerations, the synthesis of zatebradine (Scheme 6) commences with the quaternarisation of the dihydroisoquinoline **12** which was accomplished[5] under the action of a slight excess of benzylbromide at reflux of toluene. The salt **14**, isolated in high yield, was next exposed to the action of an excess of tribromomethyl anion, generated following the Duchardt and Kröhnke protocol,[6] to provide the addition product **15** in 70% isolated yield.

The stage was thus set for the crucial ring homologation reaction which was carried out by treating **15** with an aqueous solution of silver nitrate in acetonitrile as the solvent. Gratifyingly, the expected 3-benzyl-1-hydroxy-7,8-dimethoxy-1,2,4,5-tetrahydro-benzo[*d*]-azepin-2-one **10b** could be isolated[7] in 71% yield after flash chromatography purification. At this stage it is not without interest to note that: (1) initial attempts to react tribromomethyl derivatives **1** and **5** with aqueous silver nitrate in the absence of methanol gave poor yield of the expected benzo[*b*]- and benzo[*d*]azepin-2-ones **2b** and **4b**, respectively; (2) the yield for the formation of **10b** is significantly higher than the yield (45%) for its OMe analogue **10a** isolated after running the reaction in a hydromethanolic medium.

Compound **10b** was next converted to the desired lactame **9** in two high yielding steps featuring N-debenzylation (→**16**) and benzylic alcohol reduction.[8] The final assembly of zatebradine was then achieved following a known procedure,[9] that is: deprotonation of **9** followed by alkylation of the resulting anion with the chloro derivative **17** prepared by reacting the commercially available [2(3,4-dimethoxy-phenyl)-ethyl]methyl-amine (*N*-methylhomo-veratrylamine) with 1-bromo-3-chloro-ethane.

In conclusion, we have shown that treatment of the 1-tribromomethyl-1,2-dihydro-isoquinoline **5** with an hydroalcoholic solution of silver nitrate effected its transformation into the 1,3-dihydro-benzo[*d*]azepin-2-one **4a**. This ring enlargement reaction could also be accomplished with a 1-tribromomethyl-1,2,3,4-tetrahydro-isoquinoline substrate (e.g. **15**) to form 1,3,4,5-tetrahydro-benzo[*d*]azepin-2-ones (e.g. **10a** and **10b**). The potentialities of the reaction were illustrated with a new synthesis of the anti-anginal compound zatebradine **3**. It is worth mentioning that, compared to the azido-Schmidt reaction, our reaction offers additional synthetic possibilities. Further work is in progress to understand the scopes and limitations of the reaction and to best delineate its mechanism.

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2. See for instance: *Drugs of the future* **1997**, *22*, 933–934.
3. Spectral data for the 3-benzyl-1,3-dihydro-benzo[*d*]azepin-2-one **4a**: IR (KBr): 1678 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 3.59$ (s, 3H, OCH_3), 4.45 (br. s, 1H, $CHOCH_3$), 4.71 and 4.87 (AB system, 2H, $J = 15.0$ Hz, NCH_2), 6.25 (d, 1H, $J = 9.2$ Hz, CH=C*H*–N), 6.45 (d, 1H, $J = 9.2$ Hz, C*H*=CH–N), 7.05–7.15 (m, 2H-Ar), 7.20–7.35 (m, 5H-Ar), 7.44 (td, 1H-Ar, $J = 7.6$ Hz and 1.4 Hz), 7.65 (d, 1H-Ar, $J = 1.4$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 50.8, 58.3, 81.1, 117.3, 124.3, 127.0, 127.4, 127.7, 127.8 (2C), 128.4, 128.7 (2C), 129.0, 131.2, 133.7, 136.6, 166.9. MS: m/z (relative intensity) = 279 (42) [$M^{+\bullet}$], 264 (9), 220 (19), 91 (100), 65 (18). HRMS (SIMS), [$M^{+\bullet}$] calcd for $C_{18}H_{17}NO_2$: 279.1259; found: 279.1266.
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7. Experimental procedure and spectral data for the 3-benzyl-1-hydroxy-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[*d*]azepin-2-one **10b**:
   To a well-stirred suspension of the 2-benzyl-6,7-dimethoxy-1-tribromomethyl-1,2,3,4-tetrahydro-isoquinoline **15** (300 mg, 0.56 mmol) in CH_3CN/H_20 (1:1, 10mL) at −20°C was added an aqueous solution of silver nitrate (280 mg, 3 equiv.) and the mixture was allowed to warm to room temperature. After 16 h, the mixture was filtered through a short plug of Celite that was rinsed with dichloromethane. After removal of the solvents under

reduced pressure, the remained aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic layers were then washed with water (20 mL), brine (20 mL) and dried over magnesium sulfate. Removal of the solvent under reduced pressure was followed by flash-chromatography of the residue on silica gel using ethyl acetate/petroleum ether (7:3) as an eluent to give 130 mg (71%) of compound **10b** (mp: 131–132°C). IR (KBr): 3405, 1656 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.75$–3.10 (m, 2H), 3.25–3.40 (m, 1H), 3.82 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.90–4.10 (m, 1H), 4.55 (d, $J = 5.8$ Hz, 1H, C*H*OH), 4.53 and 4.84 (AB system, $J = 14.8$ Hz, 2H, N-CH_2-Ph), 5.76 (d, $J = 5.8$ Hz, 1H, CHO*H*), 6.49 (s, 1H), 7.15–7.35 (m, 5H), 7.40 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 31.4$, 45.2, 50.9, 56.0 (2C, OCH_3), 67.9, 108.3, 112.9, 125.5, 127.9, 128.1 (2C), 128.6, 128.8 (2C), 136.6, 147.7, 148.1, 173.6. MS: m/z (relative intensity) = 327 (36) [$M^{+\bullet}$], 297 (43), 206 (24), 91 (100), 77 (9), 65 (12). HRMS (SIMS), [$M^{+\bullet}$] calcd for $C_{19}H_{21}NO_4$: 327.1470; found: 327.1469.

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