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A simple route to tetrahydro-1,4-benzodiazepin-3-ones bearing diverse N1, N4, and C10 functionalization

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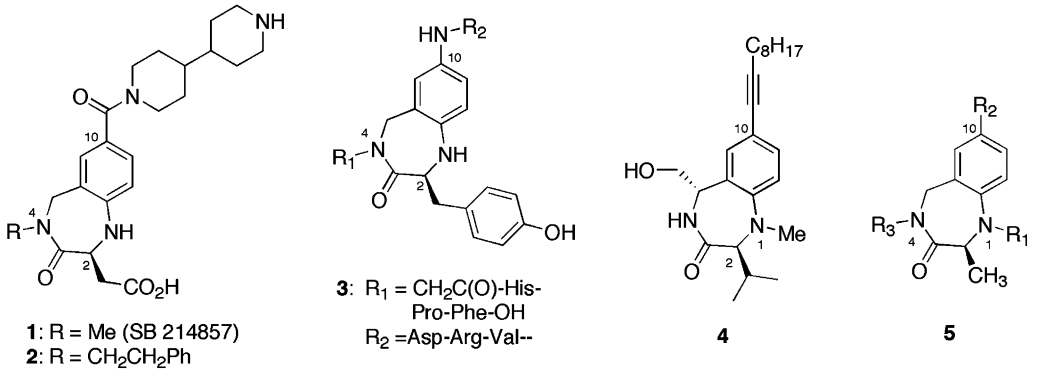
Abstract—We describe an efficient synthesis of enantiopure tetrahydro-1,4-benzodiazepine-3-ones derived from L-alanine. Diverse substitution at N1, N4, and C10 can be achieved by coupling various *N*-alkyl derivatives of L-alanine and *N*-allyl-(2-fluoro-5-nitro)benzylamine. Cyclization of this intermediate proceeds in high yield and without racemization, providing diversity at N1. The NO_2 group was easily transformed into other functional groups or removed, providing diversity at C10. Finally, oxidative deallylation allows diverse substitution to be installed at N4.

The tetrahydro-1,4-benzodiazepine-3-one scaffold has been found to be useful for the preparation of fibrinogen receptor antagonists **1**–**2**,[1–3] angiotensin analogs **3**,[4] and protein kinase C activators **4**.[5] Inspection of compounds **1**–**4** demonstrates the importance of substitution at N1, N4, C2, and C10 on this scaffold. In this letter we describe an efficient route to diversely functionalized tetrahydro-1,4-benzodiazepin-3-ones **5** derived from alanine that bear this substitution pattern (Scheme 1).

The key step in most syntheses of tetrahydro-1,4-benzodiazepin-3-ones is closure of the heterocyclic ring by intramolecular nucleophilic aromatic substitution. To accelerate substitution, a carboxyl ester[1–3] or nitro[3,4] group is most often placed *para* to the leaving group.[6] We envisioned performing a cyclization of an intermediate (e.g., **9**–**11**) that already incorporated the desired N1 substituent R_1 and an allyl group at N4 that could be subsequently deprotected and alkylated. The nitro group was chosen to facilitate nucleophilic substitution, since subsequent functional group transformation would provide diversity at C10. To assemble the cyclization precursor, we adopted the basic strategy of Miller et al.[1] However, at the outset it was not clear whether



Scheme 1. Medicinally important tetrahydro-1,3-benzodiazepin-3-ones **1**–**4** and target scaffold **5**.

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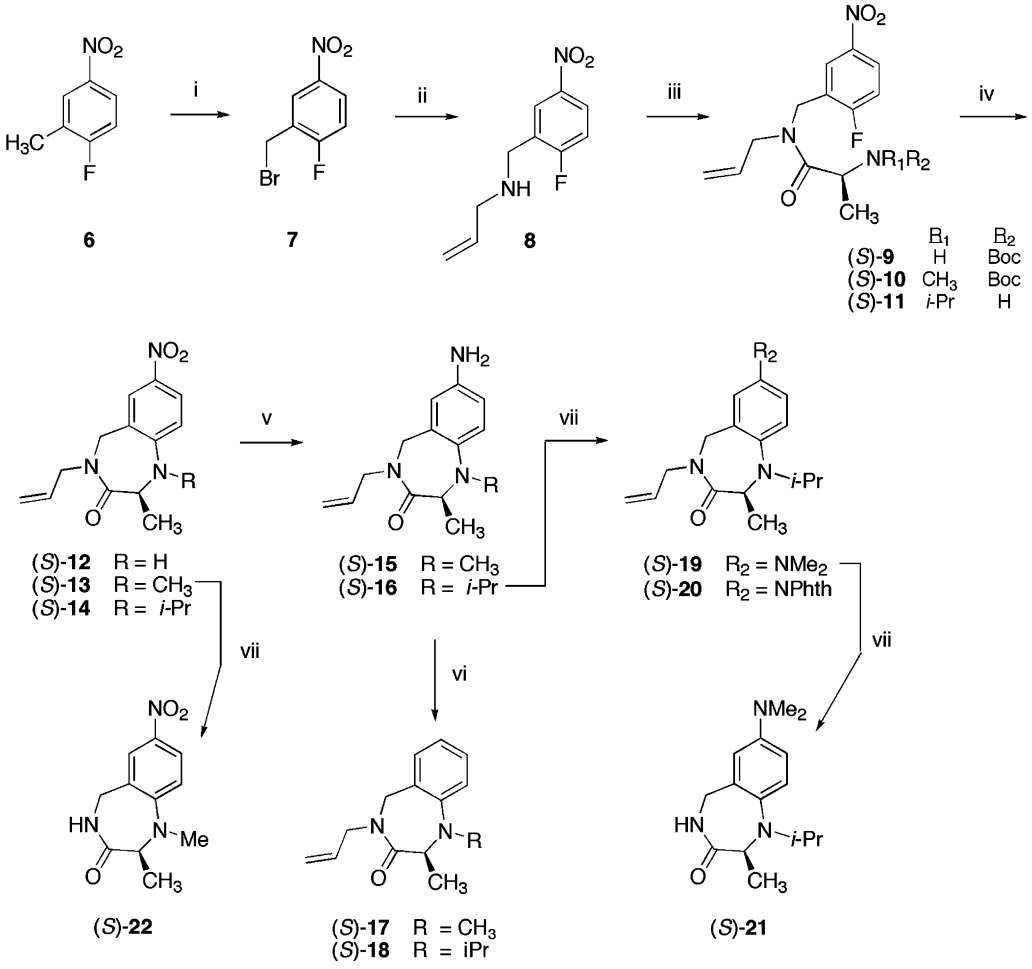
non-racemizing cyclization could be achieved with a secondary amine; the two published relevant examples (i.e., *p*-NO_2)[3,4] feature primary amines (i.e., $R_1 = R_2 = H$). Furthermore, yields are sometimes low (e.g., 18%),[3] and the basic reaction conditions might promote racemization during the long reaction times reported (12–72 h).[4]

Our syntheses began with commercially available **6** (Scheme 2); treatment with NBS in CCl_4 afforded **7** as off-white, needle-like crystals in 66% yield. Subsequent reaction with excess allylamine in THF gave **8** in 87% yield. Note that reaction of **7** with methylamine is less selective, giving significant amounts of the undesired nucleophilic aromatic substitution product. Compound **8** was then coupled with either (*S*)-*N*-Boc-Ala-OH, (*S*)-*N*-Boc-*N*-methyl-Ala-OH,[7] or (*S*)-*N*-*i*-Pr-Ala-OH[8] (DCC, HOBT in CH_2Cl_2) to afford (*S*)-**9** (86%), (*S*)-**10** (86%), and (*S*)-**11** (68%), respectively. Apparently, the *i*-Pr group is large enough to prevent significant self-condensation of the unprotected *N*-*i*-Pr-Ala-OH under these conditions. Previous syntheses of tetrahydro-1,4-benzodiazepin-3-ones from intermediates like **9** feature removal of the N1 protecting group (Boc, FMOC) in a separate step prior to cyclization under basic conditions.[3,4] However, we found that simple heating of (*S*)-**9** and **10** to 200 °C in DMSO (without base) for 30 min caused thermolysis of the Boc group and cyclization, affording (*S*)-**12** (67%) and (*S*)-**13** (92%). Thus, cyclization of (*S*)-**9** and **10** can be carried out directly without a separate deprotection step. Cyclization of *N*-*i*-Pr analog (*S*)-**11** proceeded in 61% yield, despite the steric hindrance provided by the secondary alkyl group. These reactions of **10** and **11** represent the first published syntheses of N1-substituted tetrahydro-1,4-benzodiazepin-3-ones by direct cyclization. Finally, as hoped, chiral stationary phase HPLC indicated that no racemization had occurred during the high temperature cyclizations to **12**–**14**.

Nitro compounds **13** and **14** can easily be reduced to primary aromatic amines **15** and **16** accordingly by refluxing in CH_3OH for 3 h in the presence of Fe powder and aq NH_4Cl.[9] The corresponding amines were deaminated



Scheme 2. Synthesis of diversely functionalized tetrahydro-1,4-benzodiazepin-3-ones. Reagents and conditions: (i) NBS, CCl_4, hv, 18 h (66%); (ii) allyl amine (3.0 equiv), THF, rt, 16 h (87%); (iii) (*S*)-Boc-Ala-OH or (*S*)-Boc-*N*-Me-Ala-OH or (*S*)-*N*-*i*-Pr-Ala-OH, DCC, HOBT, CH_2Cl_2, rt, 4 h, **9** (86%), **10** (86%), **11** (68%); (iv) DMSO, 200 °C, 30 min, **12** (67%), **13** (92%, 3 h), **14** (61%, 3 h); (v) Fe/NH_4Cl(aq), CH_3OH, reflux, 3 h, **15** (97%), **16** (92%); (vi) H_2SO_4/AcOH, $NaNO_2/H_2O$, $FeSO_4{\cdot}7H_2O$/DMF, 10% NaOH, **17** (57%), **18** (44%); (vii) $NaBH_4$/THF, formaldehyde/H_2SO_4, 0 °C, NaOH(s), **19** (89%), or phthalic anhydride, AcOH, reflux, 1.5 h, **20** (80%); (vii) 10 mol % $K_2OsO_4{\cdot}2H_2O$, NMO (3 equiv), $NaIO_4$ (3 equiv), dioxane–H_2O, **21** (6 h, 60 °C, 64%), **22** (18 h, 60 °C, 75%).

by use of $NaNO_2$ and Fe_2SO_4 in DMF[10] to yield (*S*)-**17** and (*S*)-**18**, respectively; HPLC analysis of (*S*)-**17** indicated 99% ee. The primary aromatic amine (*S*)-**16** was converted to the corresponding *N*,*N*-dimethylamine (*S*)-**19** in 89% yield in the presence of $NaBH_4$ and formaldehyde in THF.[11] HPLC analysis of (*S*)-**19** indicated 99% ee. Refluxing (*S*)-**16** with phthalic anhydride in acetic acid for 1.5 h[12] afforded (*S*)-**20** in 80% yield; HPLC analysis indicated 98% ee.

Removal of the *N*4-allyl group from the tetrahydro-1,4-benzodiazepin-3-ones proved more difficult than anticipated. Traditional $Pd(PPh_3)_4$ catalyzed deallylation methods, either with *N*,*N*′-dimethylbarbaturic acid,[13] or with the Et_3N/HCO_2H system recommended for imides,[14] proved completely unsuccessful. Catalysis by $RhCl(PPh_3)_3$[15] also proved ineffectual, and $RuCl_2(PPh_3)_3$ catalyzed deallylation[16] proceeded only in low to moderate yields. In the end acceptable yields were obtained with Bundle's oxidative deallylation protocol.[17] Treatment of (*S*)-**13** and (*S*)-**19** with catalytic potassium osmate in the presence of *N*-methyl morpholine *N*-oxide and sodium periodate gave (*S*)-**22** and (*S*)-**21** in 75% and 64% yield, respectively. Chiral stationary phase HPLC indicated that no racemization had occurred during the deallylation. Since alkylation of tetrahydro-1,4-benzodiazepin-3-ones at N4 is facile,[18] a variety of alkyl groups can now be installed at this position of **21**–**22**.

In summary, enantiomerically pure tetrahydro-1,4-benzodiazepin-3-ones (**12**–**22**) were synthesized from derivatives of L-alanine. The key cyclization step proceeded quickly and easily without racemization, even in the case of 2° amines (cf. **13**, **14**). Our choice of **8** as a precursor allows differential functionalization of N1, N4, and the C10-amino group. This method could be trivially extended to other amino acids and should thus facilitate synthesis of diversely functionalized 1,4-benzodiazepin-3-ones.

Acknowledgements

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