# A Trifluoroacetic Acid Catalyzed Domino Reaction as an Approach to Amino Acid Derived 2,3-Dihydro-1*H*-1,5-benzodiazepines

Saurav Bera,[a] Pancham S. Kandiyal,[b] Ravi S. Ampapathi,[b] Gautam Panda*[a]

[a] Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow 226031, UP, India
E-mail: gautam.panda@gmail.com; E-mail: gautam_panda@cdri.res.in

[b] Sophisticated Analytical Instrumental Facility Division, CSIR-Central Drug Research Institute, Lucknow 226031, UP, India

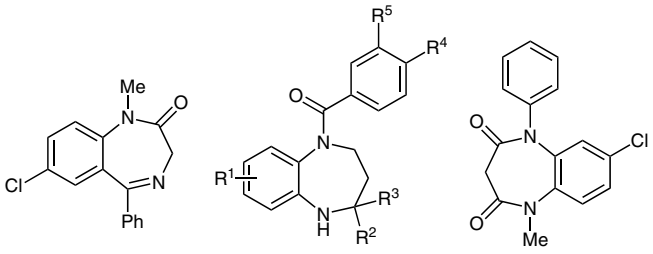
*Received: 14.12.2013; Accepted after revision: 28.01.2014*

This paper is dedicated to Prof. M. Periasamy on his 60th birthday.

**Abstract:** Trifluoroacetic acid catalyzed condensation of aromatic amines with substituted benzaldehydes followed by intramolecular cyclization furnishes a highly effective synthesis of amino acid derived 2,3-dihydro-1*H*-1,5-benzodiazepines. The strategy provides an efficient access to a library of benzodiazepines that can be explored for potential pharmaceutical or biological activities.

**Key words:** amino acids, heterocycles, benzodiazepine, domino reaction, intramolecular cyclization

Benzannulated nitrogen-containing heterocycles are core structures of numerous biologically active compounds that display a wide range of pharmacological activities.[1] Among them, benzodiazepines (Figure 1) are widely used in medicinal chemistry.[2] They belong to the class of psychotropics[3] that have notable central nervous system depressant activity,[4] along with various other biologically important activities[5] such as anticancer,[6] antiviral (HIV),[7] and cardiovascular activity.[8] Many members of this family are known as antianxiety, analgesic, antidepressive, sedative, and hypnotic agents[9] and other applications include dyes for acrylic fibers[10] and as anti-inflammatory agents.[11] In addition, 1,5-benzodiazepines are key intermediates for fused benzodiazepines, such as triaxol[12] and oxadiazol.[13]




diazepam prophylactic agent triflubazam

**Figure 1** Examples of medicinally important benzodiazepine derivatives

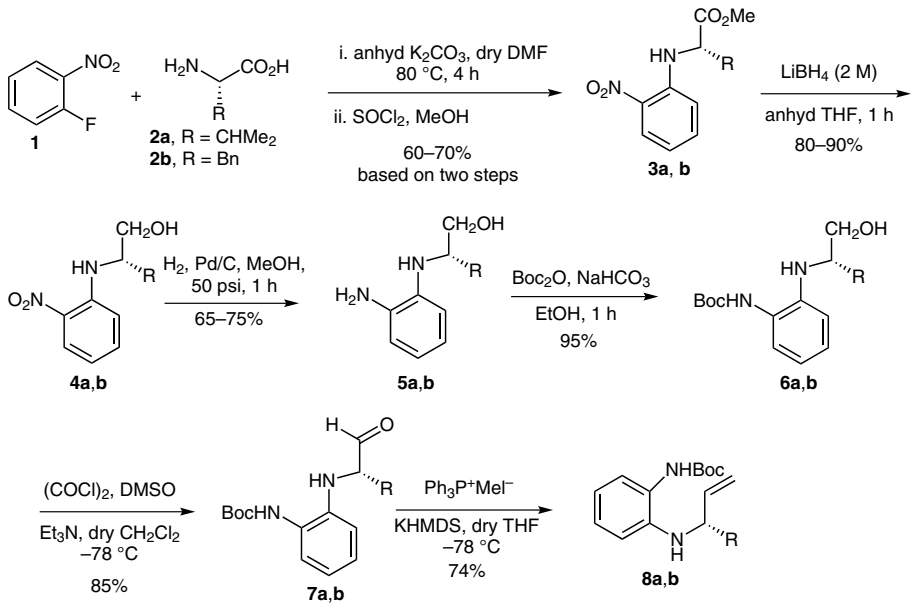
One of the most practical strategies for the synthesis of such heterocyclic compounds could be a cascade reaction in which multiple-bond formation and/or bond cleavage occurs.[14] The salient features of cascade or domino reactions are simplicity, efficiency, and shortened timing for diversity-oriented synthesis in one pot.[15] Several approaches to benzodiazepines have been reported.[16] The most general and simplest method for accessing 1,5-benzodiazepines involves the acid-catalyzed reaction of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds, β-haloketones or ketones. Many reagents including $BF_3{\cdot}OEt_2$,[17] polyphosphoric acid–$SiO_2$,[18] $NaBH_4$,[19] $MgO/POCl_3$,[20] $Yb(OTf)_3$,[21] $Al_2O_3$–$P_2O_5$,[22] and acetic acid under microwave conditions[23] have been reported for this reaction. Recently, these condensations have been reported even in monosaccharide and ionic liquid media.[24,25]

The synthesis and biology of (*S*)-amino acid based chiral heterocyles and natural product like molecules[26] have been reported by our group. Recently, we synthesized a novel series of amino acid derived benzoxazepines as potential antitumor agents[26e] and diversity-oriented benzannulated heterocyclic scaffolds employing inter- and intramolecular Mitsunobu reactions.[26g] Herein we disclose an innovative route towards the synthesis of chiral 2,3-dihydro-1*H*-1,5-benzodiazepines through an acid-catalyzed domino reaction.

(*S*)-Amino acids **2a**,**b** were reacted with 1-fluoro-2-nitrobenzene (**1**) in the presence of $K_2CO_3$ and dry DMF at 80 °C to furnish the corresponding 2-nitrophenyl N-protected amino acid derivatives which were converted into methyl esters **3a**,**b** in the presence of $SOCl_2$ and MeOH (Scheme 1). Nucleophilic aromatic substitution of 2-nitrofluorobenzene with amino acids occurs without any racemization[26h] (ee > 99%). $LiBH_4$ reduction of esters **3a**,**b** gave carbinols **4a**,**b** in 80–90% yield. The nitro group was reduced to an amine by hydrogenation to provide carbinols **5a**,**b** in 65–75% yield. Selective protection of the primary amine using Boc anhydride and sodium bicarbonate in ethanol afforded **6a**,**b** both in 95% yield. Swern oxidation at –78 °C gave aldehydes **7a**,**b** which underwent one-carbon Wittig olefination to afford **8a**,**b**.

With intermediate **8a** in hand, we targeted enantiomerically pure tetrahydro-5*H*-isoquinolino[2,3-*a*]quinoxaline **11** in one pot via an inverse electron-demand Diels–Alder reaction (Scheme 2). However, when **8a** was treated with trifluoroacetic acid (TFA) followed by addition of substituted benzaldehydes at room temperature, dihydrobenzodiazepines **12** were unexpectedly isolated instead of **11**.

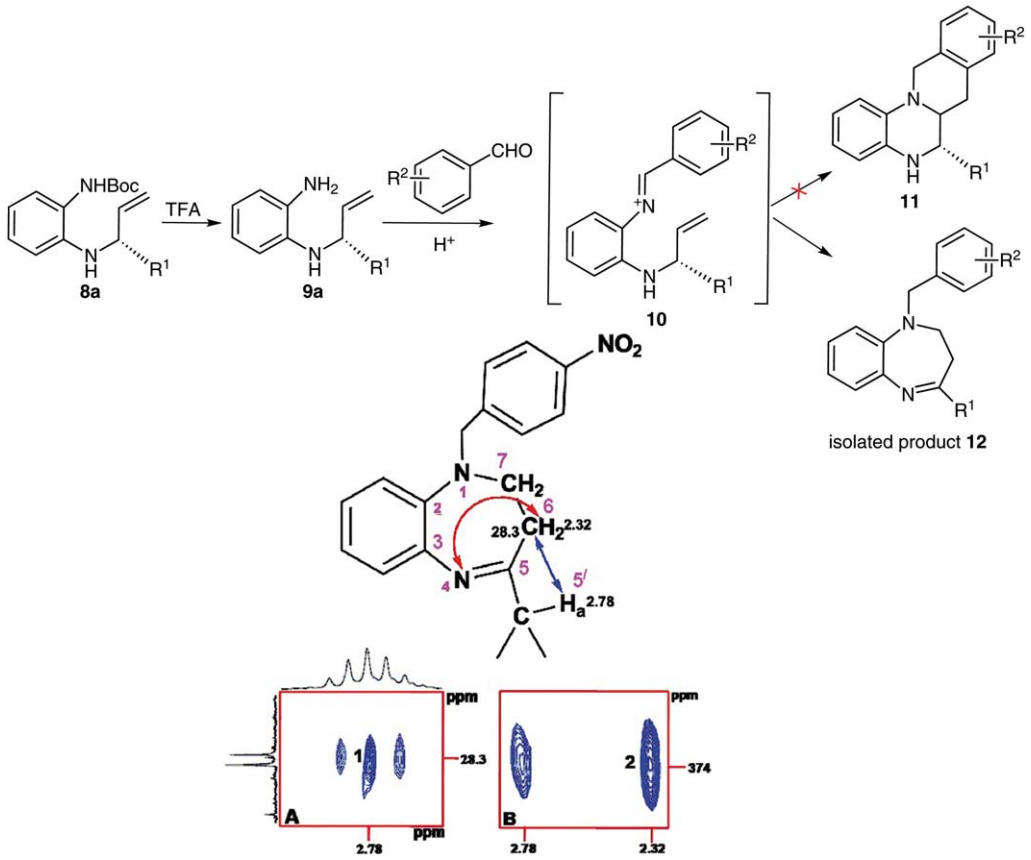
*SYNLETT* 2014, 25, 0939–0944
Advanced online publication: 11.03.2014
DOI: 10.1055/s-0033-1340837; Art ID: ST-2013-D1140-L




**Scheme 1** Synthesis of substrate **8**

This was confirmed by $^{1}H$–$^{1}H$ homonuclear, $^{13}C$–$^{1}H$ and $^{15}N$–$^{1}H$ heteronuclear long-range correlations for the representative compound **12g**. Long-range correlation between $H_{5'}$ ($\delta = 2.78$ ppm) and $C_6$ ($\delta = 28.3$ ppm), supports the seven-membered ring formation. This is further confirmed by the long-range correlation between $N_4$ and $C_6H$.

During optimization of this TFA-catalyzed domino reaction, varying solvents and stoichiometries of reagents, noticeable results were examined (Table 1). The maximum

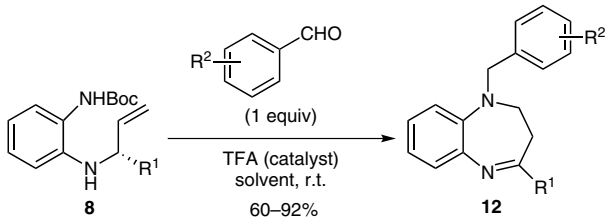



**Scheme 2** Strategy for preparation of benzodiazepines. (A) $^{13}C$–$^{1}H$ HMBC correlation of **12g** is shown between $H_{5'} \leftrightarrow C_6$ with blue arrow and labelled as **1**. (B) $^{15}N$–$^{1}H$ HMBC correlation of **12g** is shown between $N_4 \leftrightarrow C_6H$ with red arrow and labelled as **2**.

yield (92%) was obtained with two equivalents TFA at room temperature for 30 minutes. With one equivalent TFA and **8** yields were lower.

**Table 1** Screening of the Substrates and Optimization of the Reaction




| Entry | Substrate | TFA (equiv) | Solvent | Time (min) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **8a** | 0.0 | $CH_2Cl_2$ | 50 | 0 |
| 2 | **8a** | 0.1 | $CH_2Cl_2$ | 45 | 51 |
| 3 | **8a** | 1.0 | $CH_2Cl_2$ | 48 | 65 |
| 4 | **8a** | 1.5 | $CH_2Cl_2$ | 48 | 72 |
| 8 | **8a** | 2.0 | $CH_2Cl_2$ | 30 | 92 |
| 6 | **8b** | 0.1 | $CH_2Cl_2$ | 38 | 62 |
| 7 | **8b** | 1.0 | $CH_2Cl_2$ | 44 | 53 |
| 8 | **8b** | 1.5 | $CH_2Cl_2$ | 50 | 69 |
| 9 | **8b** | 2.0 | $CH_2Cl_2$ | 35 | 85 |
| 10 | **8a** | 0.1 | MeCN | 50 | 0 |
| 11 | **8a** | 1.0 | MeCN | 45 | 15 |
| 12 | **8b** | 2.0 | MeCN–$H_2O$ (1:1) | 55 | 42 |

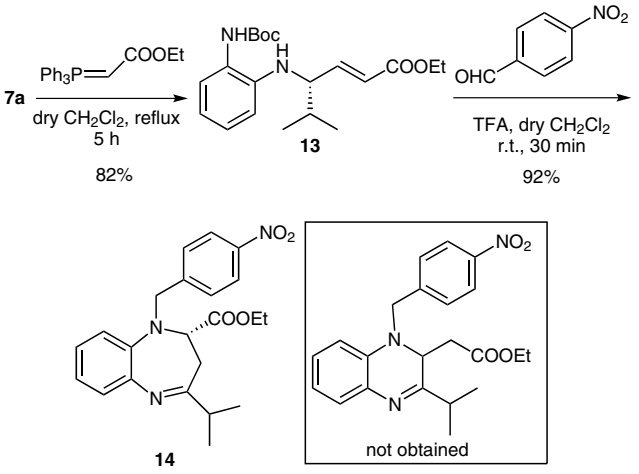
[a] Isolated yield after column chromatography.

To explore this synthetic strategy, substituted benzaldehydes with a variety of electron-releasing groups; that is, Me, OMe, and electron-withdrawing groups, such as $NO_2$ and CN, were reacted with substrates **8** under similar conditions (Table 2). The three-step reaction proceeded very efficiently under mild conditions at room temperature to produce the corresponding 2,3-dihydro-1*H*-1,5-benzodiazepines **12a**–**n** in high yields in each case.

To examine the mechanism of the reaction, further investigations were undertaken under the optimized reaction conditions. With intermediate aldehyde **7a** in hand, Horner–Wadsworth–Emmons olefination was performed in the presence of $Ph_3P{=}CHCO_2Et$ in dry $CH_2Cl_2$ to give **13** (Scheme 3). Upon treatment of **13** with 4-nitrobenzaldehyde and TFA in dry $CH_2Cl_2$, (*S*)-ethyl4-isopropyl-1-(4-nitrobenzyl)-2,3-dihydro-1*H*-1,5-benzodiazepine-2-carboxylate (**14**) was isolated. NMR analysis of compound **14** also displayed similar, long-range correlations as detected in **12g**, supporting the same mechanistic route like compound **12**.

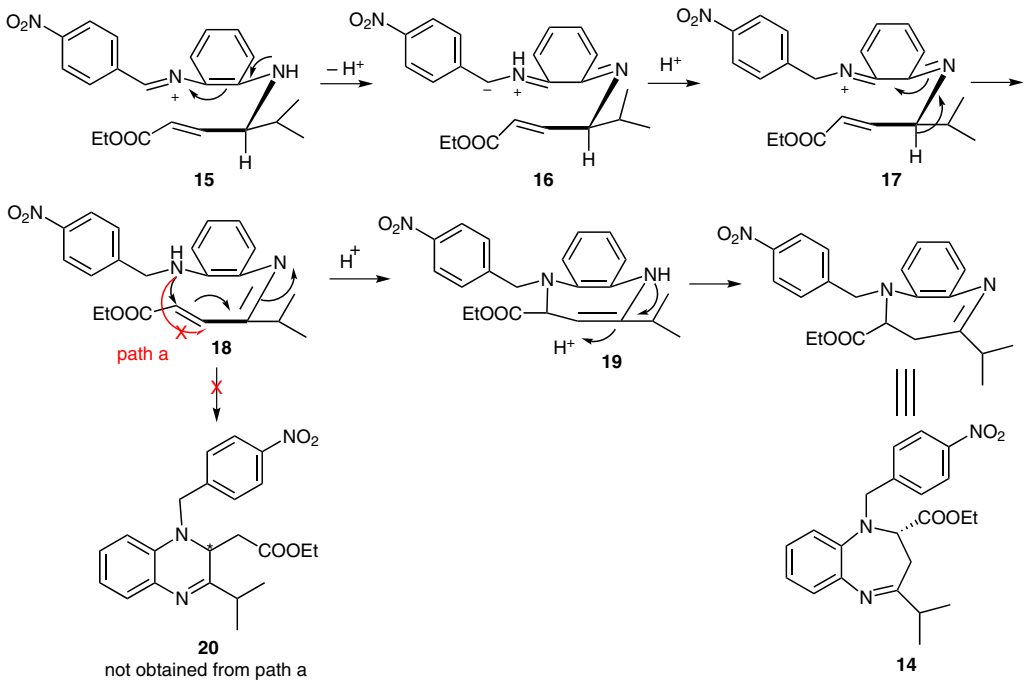
**Table 2** Synthesis of 2,3-Dihydro-1*H*-1,5-benzodiazepine

| Entry | R | ArCHO | Product | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 1 | $CHMe_2$ | 4-$FC_6H_4$ | **12a** | 35 | 89 |
| 2 | $CHMe_2$ | 4-$NCC_6H_4$ | **12b** | 30 | 92 |
| 3 | $CHMe_2$ | 2-$FC_6H_4$ | **12c** | 32 | 90 |
| 4 | $CHMe_2$ | 3-$MeC_6H_4$ | **12d** | 38 | 65 |
| 5 | $CHMe_2$ | 2-$MeC_6H_4$ | **12e** | 40 | 68 |
| 6 | $CHMe_2$ | 3-$O_2NC_6H_4$ | **12F** | 32 | 91 |
| 7 | $CHMe_2$ | 4-$O_2NC_6H_4$ | **12g** | 30 | 92 |
| 8 | $CHMe_2$ | 3-$FC_6H_4$ | **12h** | 35 | 88 |
| 9 | $CHMe_2$ | 4-$ClC_6H_4$ | **12i** | 45 | 82 |
| 10 | $CHMe_2$ | 3-$ClC_6H_4$ | **12j** | 40 | 79 |
| 11 | $CHMe_2$ | 3-thiophene | **12k** | 45 | 78 |
| 12 | Bn | 4-$NCC_6H_4$ | **12l** | 42 | 80 |
| 13 | $CHMe_2$ | 4-$MeC_6H_4$ | **12m** | 34 | 61 |
| 14 | $CHMe_2$ | 4-$MeOC_6H_4$ | **12n** | 38 | 60 |




**Scheme 3** Synthesis of compound **14**

The probable mechanism for the TFA-catalyzed transformation of compounds **8a**,**b** into benzodiazepines **12a**–**n**[27] is shown in Scheme 4. Initially, the iminium ion **15**, formed from condensation between the benzaldehyde and amine, undergoes sigmatropic 1,5-H shift (NH → CH)[28] to furnish the intermediate *o*-quinonediimine (type **16** without anion). Subsequently, intermediate **16**through another 1,5-H shift (CH → NH) generates the intermediate **18**. Of the two reaction pathway possible from **18**, intramolecular 7-*endo-trig* aza-Michael addition onto the most activated α,β-unsaturated iminium ion followed by 1,7-electrocyclization and final rearomatisation affords benzodiazepine **14**. Intermediate **18** does not furnish **20**.




**Scheme 4** Possible mechanism for the formation of product **14**

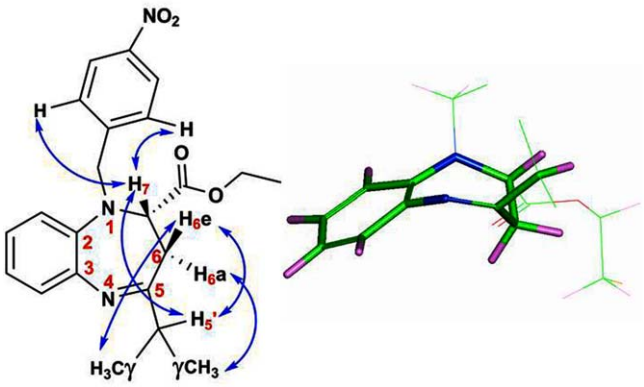



**Figure 2** Confirmation of stereochemistry of **14** by NOESY (400 MHz, $CDCl_3$). Characteristic NOE values and average structure from 1nS MD run. (A) NOE enhancements are shown in blue arrows and support the proposed twist-chair conformation of the seven-membered ring. (B) Average of the 15 lowest-energy structures resulted from the restrained molecular dynamics (MD) run. For clarity, the nitrophenyl group is replaced with a methyl group after the MD run.

For compound **14**, a vicinal coupling constant of 11.8 Hz between $H_{6a}$ and $H_7$ suggests their diaxial relative disposition. Additionally, NOE enhancements between $H_7 \rightarrow$ Ph (*ortho*), $H_{6a} \rightarrow$ Ph (*ortho*), $CH_3(\gamma) \rightarrow H_{6e}$ and $CH_3(\gamma) \rightarrow H_{6a}$ (weak) further support the proposed conformation for the seven-membered ring. Restrained molecular dynamics (MD) calculations were performed with a Discovery Studio 3.0 client program using CHARMm force field[29] with default parameters throughout the simulation. The average structure, given in Figure 2, suggests that the cycloheptadiene ring adopts the proposed twisted-chair conformation, which is flattened at the Val residue due to the double bond.

In conclusion, we have established a new strategy for the synthesis of 1,5-benzodiazepines from amino acid derived substrates and substituted benzaldehydes through TFA-catalyzed domino transformation. This synthesis proceeds via Boc deprotection, imine formation, and intramolecular cyclization to form the seven-membered heterocycle. Ths simple, convenient, easily reproducible, and high-yielding procedure for accessing functionalized 1,5-benzodiazepine scaffolds may be useful in both synthetic and medicinal chemistry.

## Acknowledgment

This research project was supported by the Department of Science and Technology, New Delhi, India. SB and PSK are thankful to CSIR for providing fellowships. Instrumental facilities from SAIF, CDRI (communication no 174/2013/GP), Lucknow is acknowledged.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## References and Notes

(1) For a book chapter: Gilchrist, T. L. In *Heterocyclic Chemistry*; Addison Wesley: Essex, England, **1997**, 3rd ed., 414.
(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
(3) Michelini, S.; Cassano, G. B.; Frare, F.; Perugi, G. *Pharmacopsychiatry* **1996**, *29*, 127.
(4) Parola, A. L.; Yamamura, H. I.; Laird, H. E. *Life Sci.* **1993**, *52*, 1329.
(5) Knabe, J.; Buech, H. P.; Bender, S. *Arch. Pharm.* **1995**, *328*, 59.