BENZOTHIAZEPINE FUSED HETEROCYCLES IV : A CONVENIENT SYNTHESIS OF BENZO[*b*][1,5]THIAZEPINES USING MCM-41(H) ZEOLITE[†]

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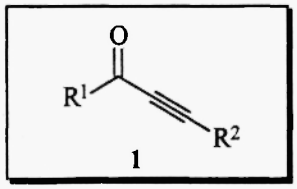
Abstract : Simple and convenient procedures have been developed for the synthesis of benzo[b][1,5]thiazepines **4**a-c by the condensation reaction between 2-amino thiophenol **2** and *tert*-butyl(4R)-2,2-dimethyl-4-(3-oxo-3-phenyl-2-propynyl)-1,3-oxazolane-3-carboxylate **3**a-c with MCM-41(H) zeolite in acetonitrile.

Introduction

A number of 1,5-benzothiazepines were found to exhibit wide range of pharmocological activities[1-10] like coronary vasodilatory tranquilizing, bactericidal, sedative, diuretic, CNS depressant, blood pressure depressant and non-hypnotic activities. Synthesis of this group of benzothiazepines has been intensely studied and numerous procedures are described in the literature.[11-14] A recent successful approach has been investigated by Villalgordo research group,[15] modification of the known reaction conditions or the development of new procedures are important to get newer insight into the formation of these 1,5-benzothiazepines.



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On the other hand, α-acetylenic ketones of type **1** have been shown to be highly versatile building blocks. These conjugated ynones have proven to be very suitable substrates for the synthesis of a wide range of heterocyclic systems,[16-23] including for instance, the synthesis of the natural product L-lathyrine and related analogues,[24] when properly functionalised, compounds of type 1 have also proven to be valuable substrates for cominatorial and parallel synthesis on solid support of highly molecular diverse 2,4,6-trisubstituted pyrimidines.[25,26] In continuation of our ongoing and previous investiations[27,28] the present aim of this study was, therefore, to introduce simple and convenient procedures for the synthesis of *tert*-butyl-2,2-dimethyl-4-(4-phenylbenzo[*b*][1,5]thiazepin-2-yl)-1,3-oxazolane-3-carboxylates by the reaction of 2-aminothiophenol with *tert*-butyl(4R)-2,2-dimethyl-4-(3-oxo-3-phenyl-1-propynyl)-1,3-oxazolane-3-carboxylates (**3a-c**)[29] in the presence of MCM-41(H) zeolite.[30-32]

Chemistry

Reaction of 2-aminothiophenol **2** with *tert*-butyl(4R)-2,2-dimethyl-4-(3-oxo-3-phenyl-1-propynyl)-1,3-oxazolane-3-carboxylates **3a-c** and MCM-41(H) zeolite in acetonitrile were heated under reflux to give expected benzo[b][1,5]thiazepines (**4a-c**) in excellent (90-92%) yields. Strucutres of compounds synthesized have been elucidated by elemental analyses, IR, ^{1}H NMR and ^{13}C NMR measurements. A C=N band characteristic for such 2,3-dihydro-1,5-benzothiazepines has been observed between 1595 and 1611 cm^{-1}. Chemical shift, coupling constant values and multiplicity of protons attached to carbon atoms C-2 and C-3 unequivocally prove the structure of all reaction products.

In summary, it can be concluded that we managed to introduce eficient procedures for the preparation of 1,5-benzothiazepines starting from α-alkynyl ketones of type **3** using MCM-41(H) zeolite.

Experimental

Melting points or boiling points of compounds could not measure due to quite unstability even at room temperature. ^{13}C and ^{1}H NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometers (chemical shifts are in δ ppm using TMS as internal standard), IR spectra were recorded in KBr on a Perkin-Elmer bio-spectrometer and elemental analyses were carried out with a Carlo Erbra Model 1106 Elemental Analyser.

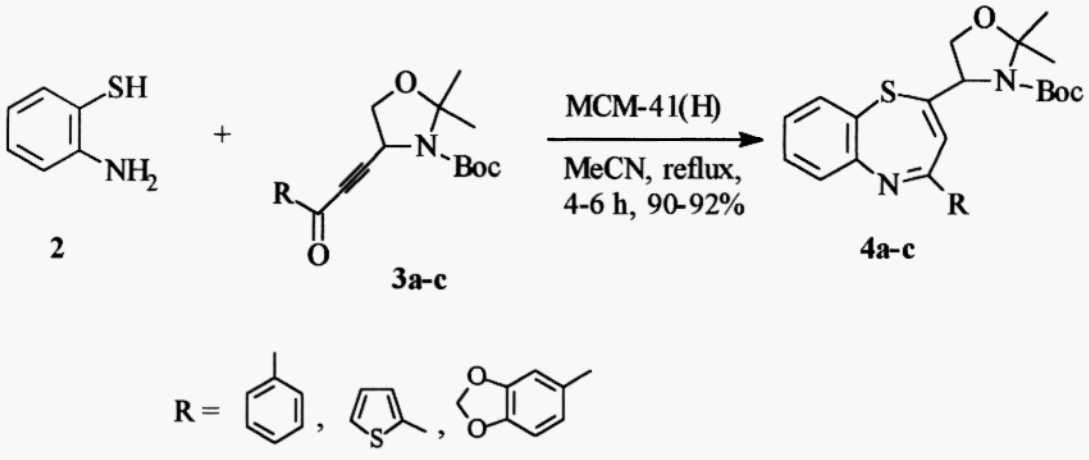
General procedure for the synthesis of compounds 4a-c

A mixture of 2-aminothiophenol (2, 0.1 mole), *tert*-butyl(4R)-2,2-dimethyl-4-(3-oxo-3-phenyl-1-propynyl)-1,3-oxazolane-3-carboxylate (3a-c, 0.12 mole), MCM-41(H) zeolite (0.01 mole) and acetonitrile (50 ml) was refluxed for 4-6 h. The reaction mixture was allowed to cool to room temperature, and filtered. Zeolite was washed with acetonitrile (2 x 10 ml). The solvent was evaporated under reduced pressure and was purified by column chromatography on silica gel (100-200 mesh, ethyl acetate-hexane 2:8) to afford:

***tert*-Butyl-2,2-dimethyl-4-(4-phenylbenzo[b][1,5]thiazepin-2-yl)-1,3-oxazolane-3-carboxylate (4a).** Yield 92%; ^{1}H NMR (DMSO-d_6) : δ 1.40 (9H, s, $(CH_3)_3C$), 1.61 (3H, s, $(CH_3)_2C$), 1.78 (3H, s, $(CH_3)_2C$), 3.95 (1H, dd, J = 9.5 & 3.5 Hz, CH_2O), 4.31 (1H, dd, J = 9.5 & 7.0 Hz, CH_2O), 4.75-4.80 (1H, m, CH), 6.76 (1H, s, CH=), 7.30-8.20 (9H, m, Ar); ^{13}C NMR (DMSO-d_6) : δ 23.8, 25.7, 27.6, 62.4, 66.9, 79.4, 94.0, 125.0, 125.6, 126.4, 126.9, 127.1, 128.0, 129.1, 130.5, 131.6, 138.3, 150.0, 150.9, 151.2, 164.2; Anal. calcd. for $C_{25}H_{27}N_2O_3S$: C, 68.93; H, 6.25; N, 6.43%. Found : C, 69.08; H, 6.28; N, 6.50%.

***tert*-Butyl-2,2-dimethyl-4-[4-(2-thienyl)benzo[b][1,5]thiazepin-2-yl)-1,3-oxazolane-3-carboxylate (4b).** Yield 90%; ^{1}H NMR (DMSO-d_6) : δ 1.43 (9H, s, $(CH_3)_3C$), 1.65 (3H, s, $(CH_3)_2C$), 1.75 (3H, s, $(CH_3)_2C$), 3.95 (1H, dd, J = 9.2 & 3.2 Hz, CH_2O), 4.31 (1H, dd, J = 9.3 & 7.0 Hz, CH_2O), 4.76-4.85 (1H, m, CH), 6.75 (1H, s, CH=), 7.32-8.00 (9H, m, Ar); ^{13}C NMR (DMSO-d_6) : δ 23.7, 25.8, 27.6, 62.5, 66.9, 79.5, 94.1, 125.0, 125.6, 126.5, 127.0, 127.1, 128.0, 129.2, 130.6, 131.8, 138.3, 141.3, 143.2, 151.2, 164.5; Anal. calcd. for $C_{23}H_{25}N_2O_3S_2$: C, 62.64; H, 5.71; N, 6.35%. Found : C, 62.65; H, 5.80; N, 6.38%.

***tert*-Butyl-4-[4-benzo[b][1,3]dioxol-5-ylbenzo[b][1,5]thiazepin-2-yl)-2,2-dimethyl-1,3-oxazolane-3-carboxylate (4c).** Yield 90%; ^{1}H NMR (DMSO-d_6) : δ 1.40 (9H, s, $(CH_3)_3C$), 1.62 (3H, s, $(CH_3)_2C$), 1.78 (3H, s, $(CH_3)_2C$), 3.96 (1H, dd, J = 9.2 & 3.4 Hz, CH_2O), 4.32 (1H, dd, J = 9.2 & 7.0 Hz, CH_2O), 4.35 (2H, s, OCH_2O), 4.78-4.82 (1H, m, CH), 6.77 (1H, s, CH=), 7.35-8.41 (7H, m, Ar); ^{13}C NMR (DMSO-d_6) : δ 23.9, 25.9, 27.6, 62.5, 66.9, 68.6, 79.5, 94.1, 125.0, 125.6, 126.5, 127.0, 127.1, 128.0, 129.2, 130.6, 131.8, 138.3, 144.0, 150.8, 151.2, 164.5; Anal. calcd. for $C_{26}H_{27}N_2O_5S$: C, 65.11; H, 5.67; N, 5.84%. Found : C, 65.12; H, 5.65; N, 5.90%.


SH
NH2
2
+
O
N
Boc
R
O
3a-c
MCM-41(H)
MeCN, reflux,
4-6 h, 90-92%
O
N
Boc
S
N
R
4a-c
R =
S
O
O

Scheme-1

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