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Synthesis of Imidazobenzazepinthiones: A New Series of HIV-1 Reverse Transcriptase Inhibitors[1]

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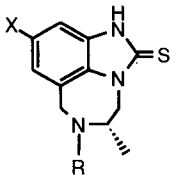
Abstract: A general route to a series of novel imidazobenzazepines that are "carba" analogs of the TIBO class of non-nucleoside HIV-1 reverse transcriptase inhibitors has been developed . A pair of allyl side-chain containing compounds were found to have significant HIV-1 inhibitory activity .

In the past several years a number of structurally diverse compound classes that selectively inhibit the action of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) have been discovered. Collectively known as the "non-nucleoside RT inhibitors" these compounds have generated substantial interest[2,3] as potential therapeutic agents for the treatment of Acquired Immune Deficiency Syndrome (AIDS). Their high enzyme specificity held out the promise of a substantially less toxic agent than the previously developed chain terminating nucleoside analogs. The first of these of inhibitors to be disclosed[4-6] was a group of tetrahydroimidazobenzodiazepinone (TIBO) derivatives. Within this group the thiones (**1**) were the most active members. The structural features key to providing high RT inhibitory activity appeared to be the sulfur of the imidazolthione, a lipophilic, unsaturated side chain R and chlorine substitution on the aromatic ring. There was no direct evidence indicating that the basic nitrogen bearing the side chain contributed to the anti-RT activity. The imidazobenzazepines with the general structure **2** were thus conceived of as prototypes for a new class of potential HIV-1 RT inhibitors. Replacement of nitrogen with carbon would allow for a variety of structural modifications not accessible in the TIBO series. The synthesis of of this "carba-TIBO" series was therefore undertaken.



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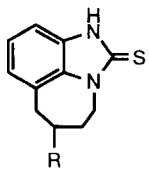
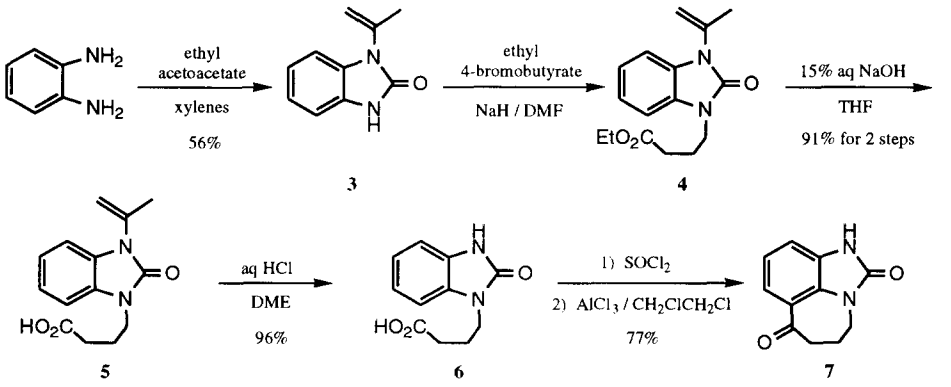


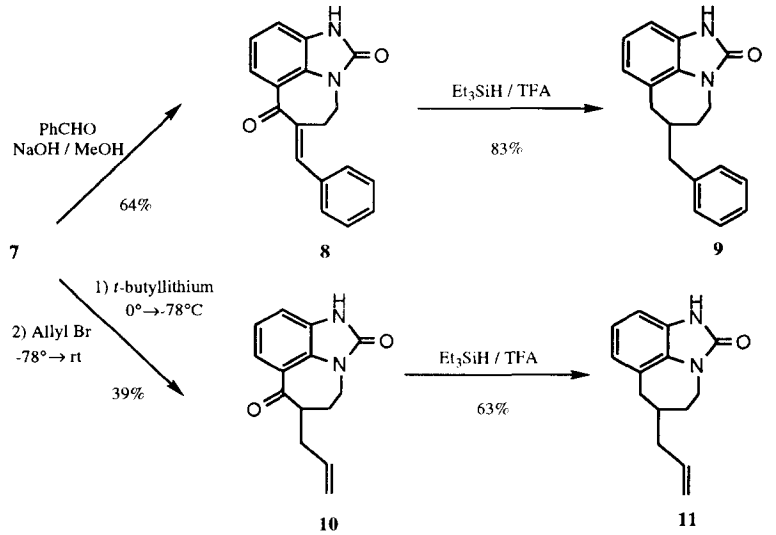
2

The desired tricyclic skeleton of **2** was seen as accessible via the cyclization of 1-benzimidazolone-4-butyric acid (**6**). Since the direct alkylation of benzimidazolone gives mixtures of mono- and dialkylated products, 1-isopropenylbenzimidazolone[7,8] (**3**) was used as the starting point for the synthesis. This mono-



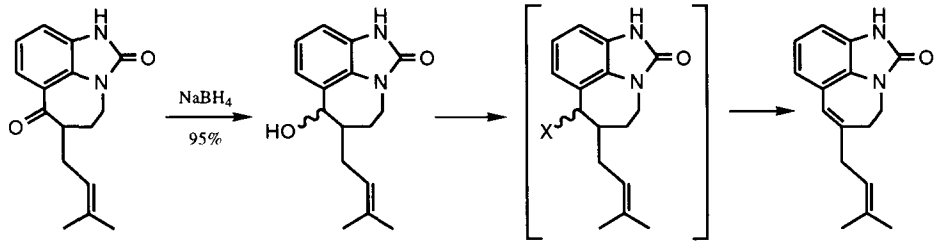
protected benzimidazolone was conveniently produced on a large scale by refluxing a solution of 1,2-phenylenediamine and ethyl acetoacetate in xylenes. The product could then be crystallized directly from the reaction mixture. Deprotonation of **3** with sodium hydride in DMF and alkylation of the anion with ethyl 4-bromobutyrate provided the ester **4**, which was then treated with 15% aq NaOH solution in THF to give the acid **5** in 91% yield for the two steps. The isopropenyl group was removed in 96% yield by treatment of a DME solution of **5** with concentrated aqueous HCl. Heating the resulting benzimidazolone **6** in polyphosphoric acid did provide the tricyclic ketone **7**, although in low yield (22%). The two step sequence in which **6** was stirred in neat thionyl chloride to provide the acid chloride followed directly by treatment with 3 equiv. of $AlCl_3$ in 1,2-dichloroethane was greatly superior, giving this central intermediate in 77% overall yield. The use of less than a threefold excess of aluminum chloride resulted in a substantially poorer conversion.

Condensation of **7** with benzaldehyde was effected with excess aq. NaOH in refluxing methanol to give the enone **8** as a single (presumably *E*) isomer in 64% yield. The enone was deoxygenated and reduced to the benzyl-substituted tricycle **9** in 83% yield by treatment with 4 equivalents of triethylsilane in TFA[9] at room



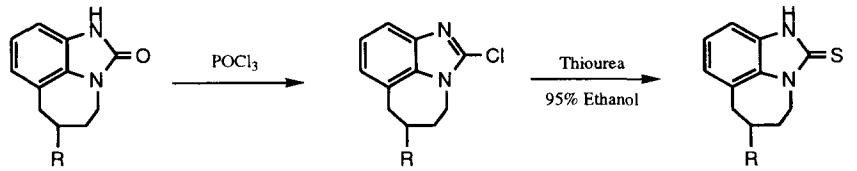
temperature. Ketone **7** could be similarly condensed with other non-enolizable aldehydes such as furfural (88%) and 3-pyridinecarboxaldehyde (79%).

Alkylation of the ketone **7** proved to be problematic. Since the alkylation of an N-protected version of **7** was seen as advantageous, the Friedel-Crafts cyclization of the N-isopropenyl acid **5** was investigated. Unsurprisingly, this reaction could not be effected cleanly and without loss of the protecting group. The NH group of **7** was successfully protected as the N-triisopropylsilyl derivative (NaH, TIPSOTf, DMF, 64% yield), however alkylation of its LDA generated enolate provided at best 1:1 mixtures of mono- and di-alkylated products. N,N-dimethylhydrazones are known to undergo selective monoalkylation[10] but this derivative of **7** could not be produced in useful quantities even under forcing conditions, presumably due to unfavorable steric interactions in the product. Optimal conditions for the production of monoalkylated ketones were found to involve formation of the dianion of unprotected **7** with one equivalent of *t*-butyllithium in a 4:1 mixture of THF and HMPT for 15 min at 0°C followed by a second equivalent for three hours at -78°C. Treatment of this dianion with 1 equivalent of allyl bromide for 3.5 hours, then warming to room temperature provided **10** in 39% yield (along with an 18% yield of the diallyl material). Deoxygenation of **10** with 3 equivalents of triethylsilane in TFA provided the carba-TIBO analog **11**[11] in 63% yield.



12 **13** **14**

In the TIBO series one of the side chains leading to the greatest HIV-1 RT inhibition is the 2-methyl-2-butenyl (prenyl) group. The alkylation of the dianion of **7** using prenyl bromide was successful, furnishing the analog **12**, however numerous attempts at deoxygenation of this material failed to provide useful product. Triethylsilane/TFA treatment as above resulted in destruction of the trisubstituted double bond. Attempted deoxygenations with $PdCl_2/NaBH_4$[12] and $ZnI_2/Na(CN)BH_3$[13] also gave products no longer containing the prenyl double bond. The ketone could be reduced with sodium borohydride in high yield (95%) to the diastereomeric mixture of alcohols **13** but attempted conversion to sulfonates or halides resulted in immediate elimination to the diene **14**. Conversion of **13** to the corresponding thiocarbonylimidazolides and subsequent treatment with tributyltin hydride provided some of the desired product but as a mixture with **14**.



7 R = H
9 R = benzyl
11 R = allyl

15 R = H
16 R = benzyl
17 R = allyl

18 R = H
19 R = benzyl
20 R = allyl

The imidazobenzazepinones **7**, **9** and **11** were converted to the corresponding chlorides **15**, **16**, and **17** in refluxing phosphoryl chloride. Although these chlorides could be isolated and purified, they are somewhat moisture sensitive and their purification provided no advantage in the subsequent transformation. Heating the chlorides with thiourea in 95% ethanol provided the thiones **18**, **19**[14], and **20**[15] in 80%, 35% and 60% yield respectively for the two steps.

Biological Activity

Of the compounds described here three showed the desired biological activity. The allyl side-chain compounds **11** and **20** both inhibited HIV-1 growth *in vitro* with IC_{50}'s of 1-2 μM. It is interesting to note that in contrast to the TIBO series of inhibitors there is no significant difference in the activity of the oxygen and sulfur analogs in the carba-TIBO series. The benzyl side-chain thione **19** did not show any activity against HIV-1 *in vitro* but it did inhibit isolated HIV-1 RT 61% at a concentration of 100 μM.

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15. For **20**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 6.91-7.11 (m, 3H), 5.76-5.89 (m, 1H), 5.06-5.12 (m, 2H), 4.69 (ddd, J = 2.8, 7.6, 14.3 Hz, 1H), 4.15 (ddd, J = 2.7, 9.7, 14.3 Hz, 1H), 3.14 (dd, J = 3.3, 16.2 Hz, 1H), 2.90 (dd, J = 8.5, 15.9 Hz, 1H), 2.16-2.33 (m, 3H), and 1.78-1.86 (m, 1H); MS (m/z): 244 (M^+).

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