HIV REVERSE TRANSCRIPTASE INHIBITORS: A CONCISE ENE REACTION BASED SYNTHESIS OF THE 7,8-DIHYDRO-6*H*,12*H*-AZEPINO [2,1-*b*] QUINAZOLINE SYSTEM, AND ITS REACTION WITH NITRILE OXIDES

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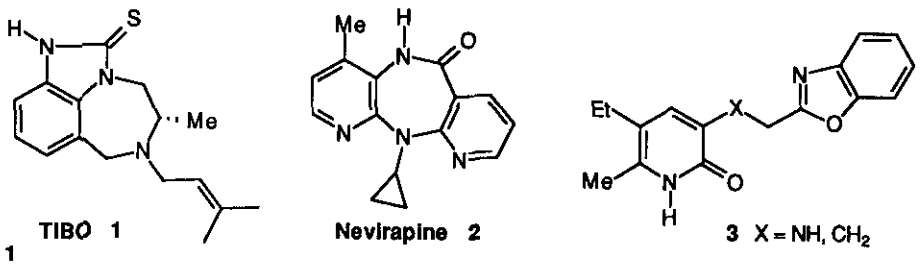
Abstract- The reaction of amide (**5**), obtained in two steps from 2-amino benzophenone (**4**) with triflic anhydride, followed by treatment of the *in situ* generated imodyl triflate (**7**) with LiCN led to exclusive formation of the tetrahydroquinazoline (**10**). Thermolysis of this intermediate promoted an ene reaction leading to the azepino-quinazoline (**11**) (63% yield). The 1,3-dipolar cycloaddition between this product and nitrile oxide (**12**) proved chemoselective, producing the novel pentacyclic oxadiazine (**14**) as a 7:3 mixture of diastereomers in 79% yield.

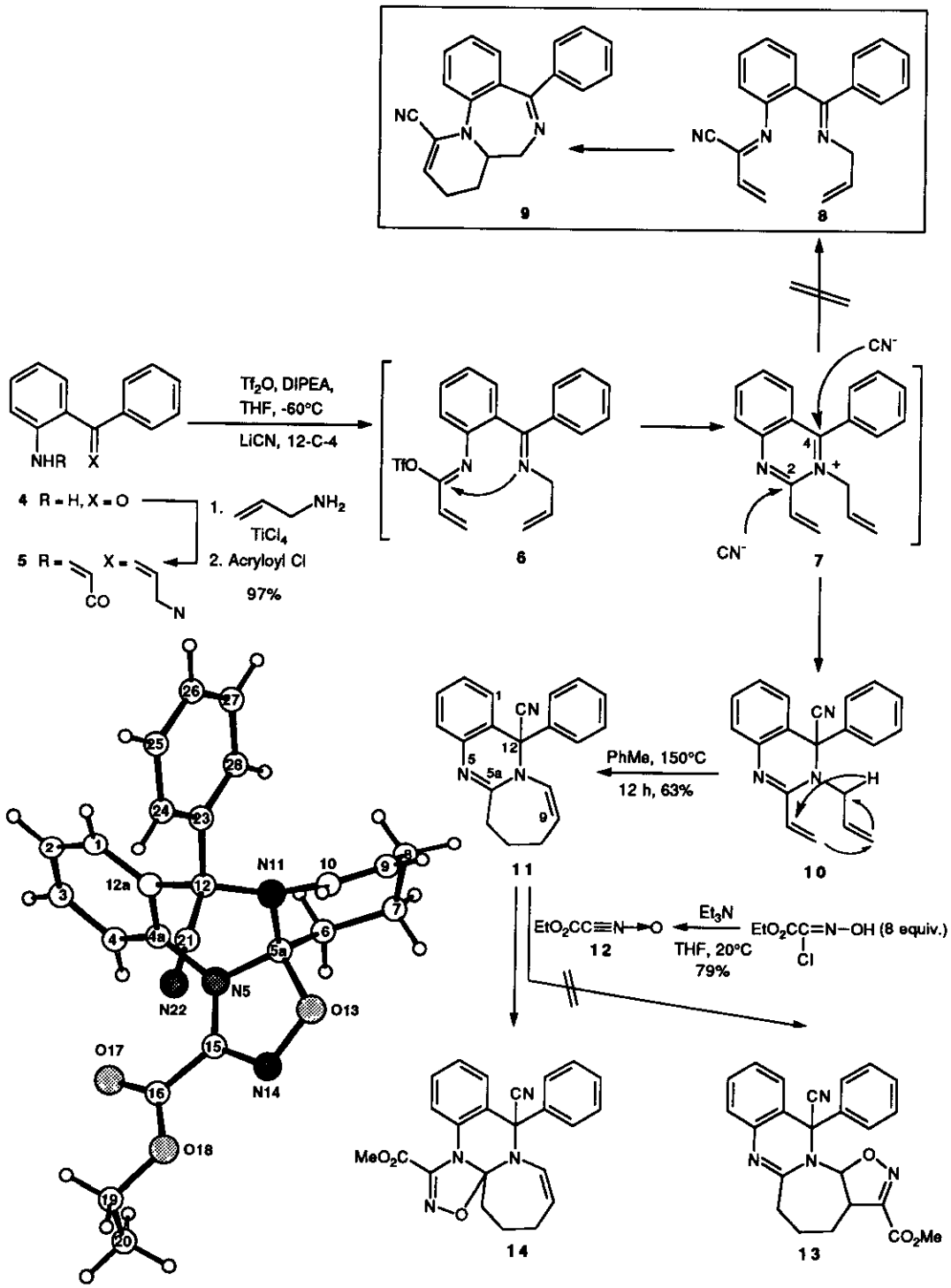
The last five years have witnessed the discovery of a number of powerful, non-competitive, inhibitors of HIV-1 reverse transcriptase (RT), including TIBO (**1**), nevirapine (**2**), and the Merck pyridinone (**3**) (Scheme 1), which bear no structural relation to nucleosides.[1-3] The rapid emergence of resistant strains to these compounds[4], however, limits their utility in the treatment of AIDS victims, and underscores the importance of finding new RT inhibitors for use in the development of regimes in combination therapy. Considering the importance of the interaction of the aromatic components in compounds (**1-3**) with the Tyr-181 and Tyr-188 residues in the allosteric site in RT-1,[4] and the presence of a benzodiazepine system in **1** and **2**, we initiated a program to prepare the novel tetracyclic 1,4-benzodiazepine (**9**) (Scheme 2). Simultaneous formation of the six and seven membered rings in **8** *via* a Diels-Alder reaction of 1-azadiene (**8**) was the projected key step in this synthesis. Indeed, recent work from our laboratories demonstrated the capacity of *N*-phenyl-2-cyano-1-azadienes to undergo Diels-Alder reaction with a complete range of dienophiles, and further showed that the Δ^2-piperideine products can be isolated by conventional column chromatography techniques.[5] As described in this paper, preliminary efforts to impliment the hetero Diels-Alder route to **9** has unveiled a competing, and efficient ene reaction pathway leading to azepino-quinazoline (**11**). Reaction of this "*N*-acyl enamine", obtained in only four steps from **5**, with nitrile oxide (**12**) was studied in an attempt to prepare the rigidified pyridinone analogue (**13**).



Scheme 1

The starting amide (**5**) for this work was prepared in high overall yield (97%) by successive reaction of 2-aminobenzophenone (**4**) with allyl amine in the presence of $TiCl_4$ and acyrolyl chloride (K_2CO_3, PhMe, 20°C). Using our standard protocol,[5] amide (**5**) was treated with triflic anhydride in CH_2Cl_2 containing diisopropylethylamine (DIPEA) at -60°C. After one hour a suspension of LiCN in THF containing 12-crown-4 was added, and stirring at -60°C was continued for an additional 45 min, before warming to -20°C and extractive work-up. From the spectral data [^{13}C nmr: δ 66 (C-4), 152 (C-2); ir: 1628 cm^{-1}] it was clear that the product of this reaction, isolated in 63% yield after silica gel flash column chromatography, corresponded to tetrahydroquinazoline (**10**), and not to the expected 2-cyano-1-azadiene (**8**). To account for the formation of **10**, one can invoke reaction of the imine nitrogen with the imodyl triflate moiety in intermediate (**6**) followed by addition of CN^- at C-4 of the resultant iminium ion (**7**). Alternatively, addition of cyanide ion to the imine in **6** may preceed cyclization. However, the first scenario is not only more likely, but also suggests a way to transform **10** into azadiene (**8**) and ultimately obtain benzodiazepine (**9**). We thus envisaged heating **10** at 150°C in toluene, as it is known that under these conditions α-aminonitriles can thermally revert to their precursor imines (iminium ions).[6] It was hoped that CN^- would then add to **7** at C-2 to give an intermediate which would undergo further transformation to azadiene (**8**) through elimination of the positively charged nitrogen substituent. However, heating **10** in toluene for 12 hours opened up a lower energy ene reaction pathway leading to formation of the interesting seven membered ring heterocycle (**11**) in 63% yield. From the 2D ^{13}C-^1H spectrum for **11** the C_9-H [δ 5.60-5.72 (m); δ 121.91] and C_{10}-H [δ 5.79 (d, J = 10 Hz); δ 129.17] signal were readily assigned.

The presence of the enamine double bond in azepine (**11**) provided a convenient starting point for the construction of an additional ring onto the molecule. In this way a series of rigid cyclic analogues of pyridinone (**3**) could be prepared which may display anti-HIV activity. To explore this idea compound (**11**) was reacted with the *in situ* generated nitrile oxide (**12**)[7] at room temperature (THF, 7 h). However, reaction with this 1,3-dipole occurred exclusively at the C=N bond to give the oxadiazoline (**14**) as an inseparable 7:3 mixture of diastereoisomers in 79% yield. The formation of compounds (**14**), rather than the the regioisomeric imine cycloaddition adduct[8] or the desired pyridinone analog (**13**) was evident from the ^1H and ^{13}C nmr data (signals for the $\Delta^{9,10}$ double bond; δ 108 for C-15). From this result it was concluded that, whereas the enamine component in **11** possesses the least substituted double bond, its efficacity as a dipolarophile is considerably diminished through conjugation with the imine system.


NC
N
N
9
NC
N
N
8
CN⁻
Tf2O, DIPEA,
THF, -60°C
LiCN, 12-C-4
NHR X
TfO
N
N
6
4
N
2
N+
CN⁻
7
4 R = H, X = O
1. NH2
TiCl4
5 R = X =
2. Acryloyl Cl
CO
N
97%
CN
1
5
N
5a
12
9
PhMe, 150°C
12 h, 63%
CN
N
N
H
10
11
EtO2CC≡N→O
12
Et3N
THF, 20°C
79%
EtO2CC=N–OH (8 equiv.)
Cl
MeO2C
CN
N
N
N
O
14
CN
N
N
O
N
CO2Me
13
26
27
25
28
24
23
2
1
3
12a
12
N11
10
9
8
7
4
4a
21
5a
6
N22
N5
O13
O17
15
16
N14
O18
19
20

Scheme 2

Subsequent confirmation of the structure of the major isomer of oxadiazoline **(14)**, recrystallized from MeOH was made by X-ray diffraction. In the ORTEP representation (Scheme 2) one sees that the central six membered ring is boat shaped with the C-5 and N-11 atoms out of the mean plane defined by atoms N-5, C-12 and the phenyl ring by 0.88 (1) and 1.00 (1) Å, respectively. In contrast, the azepine ring adopts a chair type conformation with C-6 [-0.61(2) Å], and the double bond carbons-9, and 10 [0.96(2) Å] located out of the plane determined by the four other ring atoms. The oxadiazoline ring and the carboxy residue rest essentially in the same plane (maximum deviation 0.11 Å) with the ester ethyl substituent turned 93° toward the outer surface of this system. Important also was the observation that one face of the enamine double bond is "protected" by the phenyl side chain, whereas the other side is in an unhindered environment.

Compounds **(11)** and **(14)** were tested *in vitro* for their ability to inhibit the replication of HIV-1 in CEM cells. However, neither of these heterocycles exhibited significant anti-HIV activity. Further work is in progress to direct the reaction of "N-acyl enamine" **(11)** with 1,3-dipoles toward the enamine double bond. The results of these studies will be reported at a latter date.

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Dedicated to Dr. Arnold Brossi on the ocassion of his 70th birthday

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