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Efficient synthesis of nevirapine analogs to study its metabolic profile by click fishing

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ABSTRACT

Knowledge of the biotransformation and pharmacokinetics of the antiretroviral agent nevirapine is still insufficient. In order to trace rash inducing metabolites of nevirapine, we devised a short and efficient multi-gram synthesis of a nevirapine analog that can be coupled to azide containing compounds by click chemistry.

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor (Fig. 1) currently used in the treatment of HIV.[1] It is known that NVP causes cutaneous adverse reactions with an incidence of 16% with occasional serious side effects such as Stevens–Johnson syndrome (SJS) or SJS/toxic epidermal necrolysis transition syndrome occurring with a probability of 0.3%.[2] In rat and human, NVP is metabolized into several metabolites of which 12-hydroxynevirapine has been proposed to be converted into a quinone methide reactive metabolite.[3]

In order to determine which reactive metabolites could be involved in adverse reactions and to identify which macromolecules are targeted by reactive metabolites, we have synthesized a NVP derivative that can be used to trace nevirapine metabolites in biological systems. With a tethering application in mind, a NVP analog containing an anchorage site was designed. In a previous study it was demonstrated that Et-NVP (Fig. 1), a NVP analog in which the cyclopropyl was substituted by an ethyl group did not affect the ability of the drug to cause cutaneous rash similar to NVP.[4] For this reason, we expect that the alkyne NVP analog **1** (Fig. 1) will behave like its isosteric Et-NVP and thus retain the in vivo adverse side effect. Moreover, the terminal alkyne group is an appropriate site for reaction with azide conjugated probes using click chemistry adapted to biological media (Fig. 2).[5] This article describes the synthesis of the nevirapine propargyl analog **1** and demonstrates its reactivity towards azides.

Two ways were originally envisaged to synthesize **1** and other analogs substituted at position 11 (Fig. 3).[6] Either the 2,2′-dihaloamide could react (addition then cyclization) with the suitable amine or the diazepine-like core could be alkylated at position N11.

Propargyl alcohol **2** was transformed quantitatively into its TMS derivative **3**[7] by means of *n*-BuLi and TMSCl (Scheme 1). Replacement of the alcohol by a bromide yielded **4** (78%),[8] whose bromide

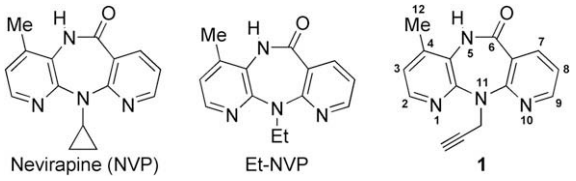

Figure 1. Structures of Nevirapine, Et-NVP and **1**.

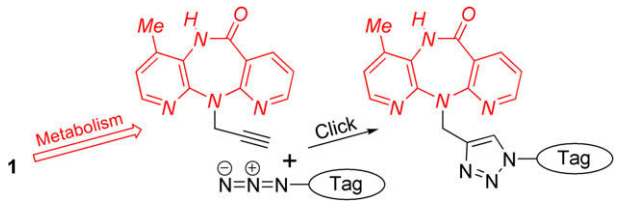

Figure 2. Click fishing principle of metabolites of **1**.

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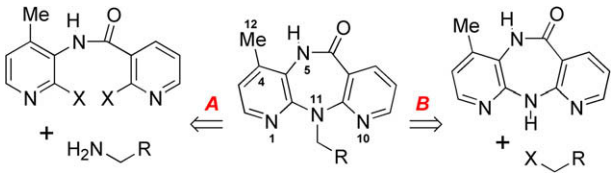
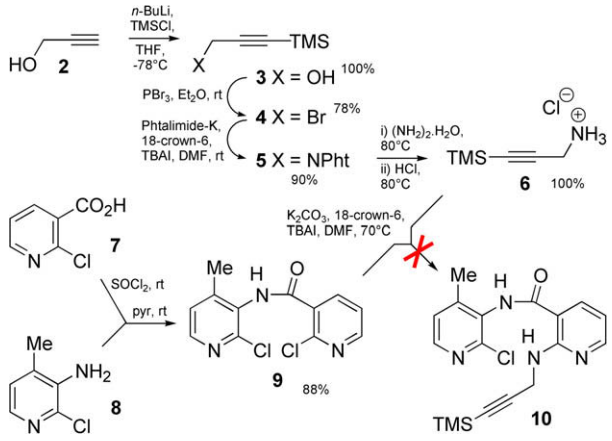


Figure 3. Retrosynthetic routes to **1** and 11-substituted analogs.



Scheme 1. Tentative synthesis of **10**.

atom was S_N2 displaced with potassium phtalamide to give **5** (90%).[9] Hydrazine treatment of **5** gave the ammonium salt **6** quantitatively. Acid **7** was activated as its acid chloride and reacted with aniline **8** to give amide **9** (88%).[5a,10] All attempts to prepare **10**, by addition of **6** to **9** remained fruitless.

Since route A (Fig. 3) via a S_NAr reaction—Chichibabin cyclization[11] sequence had failed, route B remained the only alternative. PMB-NH_2 **11** added swiftly to **9** to yield **12** (49%) whose cyclization produced **13** (88%) in THF and with NaHMDS as a base (Scheme 2).

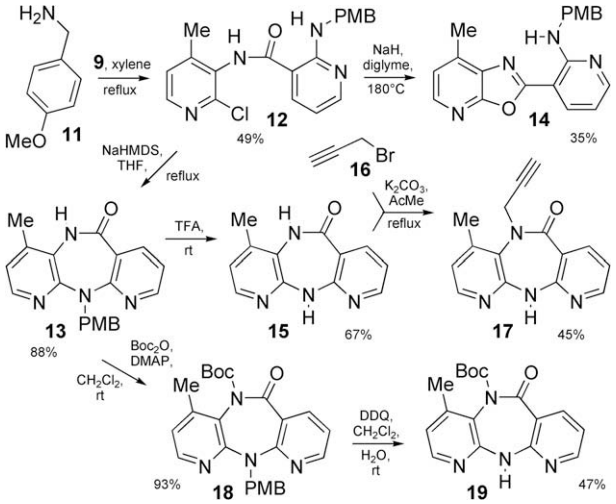
When the reaction was run with NaH in diglyme instead of NaHMDS, a tricyclic compound **14** resulted, although NaH in diglyme was a known procedure to avoid this unwanted cyclization.[12] Tricycle **15** was prepared from **13** by simple TFA treatment (67%) to check if it was possible to find selective N11 alkylation conditions. However, only N5 alkylation occurred when the anion of **15** was left to react with propargyl bromide **16** to give the propargyl derivative **17** (45%). This alkylation of **15** at the wrong position was confirmed by theoretical calculations (GAMESS).[13] The N5 anion is more stable than the N11 anion by as much as 9.1 kcal mol^{-1} (B3LYP/6-31+Gd).[14]

Without doubts **15** would never yield the desired compound **1**, unless its dianion was the reactive nucleophile. Since such direct transformation had been achieved in very low yields on related systems, it was abandoned.[6a] It became obvious that the N5 site had to be protected to alkylate selectively at the desired N11 position. The Boc protective group was introduced on amide **13** (88%). The PMB protective group located at position 11 could be removed by means of DDQ,[15] but the yield was moderate (47%) and the reaction was excessively time consuming (2 days without even reaching completion). Owing to our desire to establish a multi-gram scale synthesis for target **1**, this latter step was much too low-yielding to be really useful. Therefore, we looked for an alternative N11 protective group that would be easily cleaved.

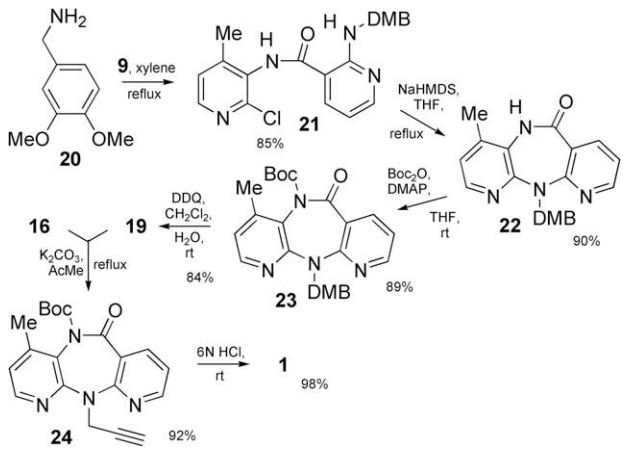
The 3,4-dimethoxy benzyl amine **20** (DMB-NH_2) was introduced in much the same way as PMB-NH_2 **11** was coupled to **9** (Scheme 3). The substituted aniline **21** was obtained with an excellent yield (85%) and was further cyclized by means of NaHMDS in THF to yield the seven-membered ring **22** (90%) without traces of its five-membered ring competitor. Compound **19** was then prepared from **22** following the same two-step sequence as that used to make **19** from **13**. Cleavage of the DMB protective group occured with ease with DDQ.[11] Compound **19** was coupled with **16** using K_2CO_3 as a base (92%) to produce propargylamine **24**.[16] Carbamate cleavage with aqueous 6 N HCl, immediately followed by $NaHCO_3$ provided target **1** neatly (98%).

We had recourse to these atypical Boc cleavage conditions because the usual procedure (TFA in CH_2Cl_2) did not produce the expected product **1** from **24**. Instead, a 85:15 mixture of two very polar and unseparable yellow compounds **25** and **26** (Scheme 4). Compound **25** slowly crystallized from the oily residue obtained after removal of solvent (Fig. 4).

Upon addition of TFA in CH_2Cl_2, a medium of low dielectric constant, the two pyridine nitrogen atoms of **24** get hydrogen bonded to TFA.[17] Consequently, both nitrogen atoms remain sufficiently nucleophilic; they can attack the neighboring alkyne group in a 5-*exo*-*dig* fashion[18] with concomitant proton delivery. The reaction is very quick as observed by the yellow coloration that starts appearing almost immediately after addition of TFA. It is likely that Boc cleavage remains faster since the outcome of the reaction is the same whenever starting from **1** or **24**. In all cases N10 undergoes cyclization preferentially over N1. This behavioral difference can be explained in terms of residual nucleophilicity of these nitrogen



Scheme 2. First synthesis of **19**.



Scheme 3. Final synthesis of **1**.