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Effects of nitrogen and alkene substitution on the $PtCl_2$ catalyzed cycloisomerization of *N*-tethered 1,6-enyne precursors to the triple reuptake inhibitor GSK1360707

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ABSTRACT

The effects of nitrogen and alkene substitution on the cycloisomerization of *N*-tethered 1,6-enynes into 3-azabicyclo[4.1.0]heptene precursors to the triple reuptake inhibitor GSK1360707 are described. In general, electron donating substituents proved beneficial both in terms of the reaction rate and chemoselectivity.

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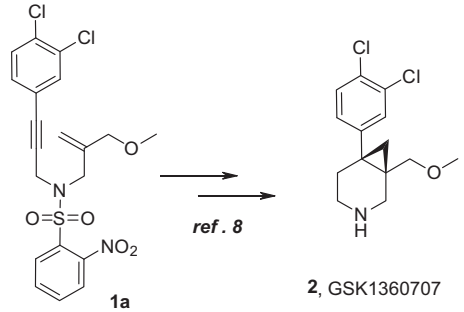
1. Introduction

The cycloisomerization of 1,*n*-enynes and related compounds has rapidly emerged as a powerful tool for the synthesis of complex polycyclic compounds of structural[1] and biological interest[2] and has been the subject of a number of mechanistic[3,4] and computational studies.[5] For substrates where the reactive partners are tethered by a nitrogen atom, the latter is typically protected as the *p*-toluenesulfonamide (tosylate, *p*-Ts).[6] Depending on other functionality present in the molecule, however, the *N*-tosyl protecting group can be difficult to cleave selectively.[7] Thus, while ideal for methodology development purposes, it can prove problematic should its removal be required. To the best of our knowledge, the effect of the nitrogen protecting group on reaction rate, chemoselectivity or further processing post-cycloisomerization has not been studied systematically for this class of substrates. Moreover, examples where the alkene fragment bears a heteroatom substituent are relatively rare.

2. Results and discussion

During the course of developing an enyne cycloisomerization route[8] to the triple reuptake inhibitor GSK1360707[9] (**2**, Scheme 1), we were interested in exploring the scope of this key reaction, both in terms of the protecting group on nitrogen, as well as the alkene substitution pattern. From the point of view of large-scale drug substance synthesis, we sought operationally facile transformations that maximize yield, minimize impurity formation, and increase material throughput. Thus, our substrate selection was guided by the potential for straightforward ultimate conversion to GSK1360707. Herein, we wish to report our findings regarding nitrogen and select alkene substituent effects on the enyne cycloisomerization reaction.

The former objective was readily accomplished by first cleaving the 2-nitrobenzenesulfonamide group in **1a** (Scheme 1, synthesized in three steps as reported previously) using modified Fukuyama



Scheme 1. Our previously reported enyne cycloisomerization approach to GSK1360707.

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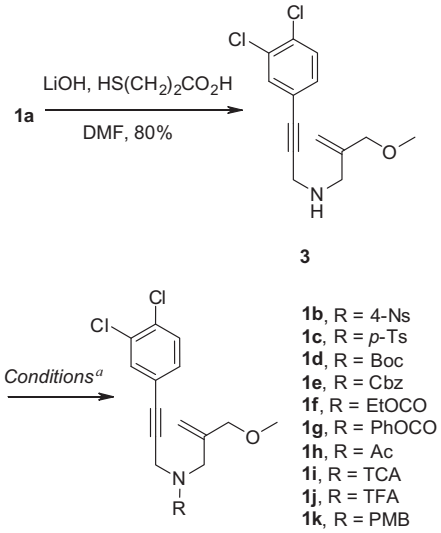
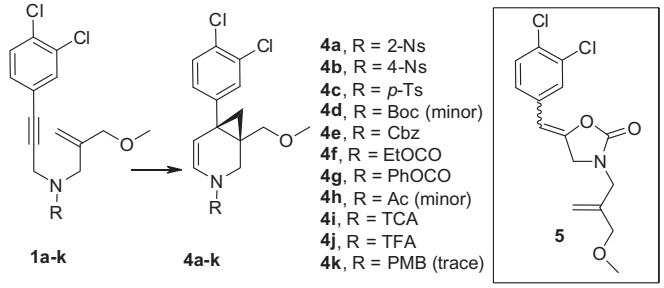


Scheme 2. Synthesis of various *N*-protected enynes. [a]Reaction conditions (all in CH_2Cl_2, 2 h, rt): **1b**, **c**, **e–i** RCl, TEA; **1d**: $(Boc)_2O$, TEA; **1j**: TFAA, TEA; **1k**: *p*-MeOPhCHO, $NaBH(OAc)_3$.

Table 1
Protecting group comparison[a]



Entry	Substrate	Major product	Time (h)	Yield[b] (%)
1	**1a**	**4a**	7	94
2	**1b**	**4b**	12	93
3	**1c**	**4c**	4.5	96
4	**1d**	**5**	2.5	83
5	**1e**	**4e**	3	91
6	**1f**	**4f**	3	90
7	**1g**	**4g**	3.5	88
8	**1h**	Mult. prod.	3	N/A
9	**1i**	**4i**	16	91
10	**1j**	**4j**	48	90
11	**1k**	Decomp.	5	N/A

[a] Reaction conditions: 10 mol % $PtCl_2$, toluene (10 ml/g **1**), 80 °C.
[b] HPLC percent area under the curve (AUC), excluding toluene peak.

conditions (LiOH, $HS(CH_2)_2CO_2H$, DMF).[10] The resulting secondary amine was then derivatized with a variety of protecting groups, as shown in Scheme 2.

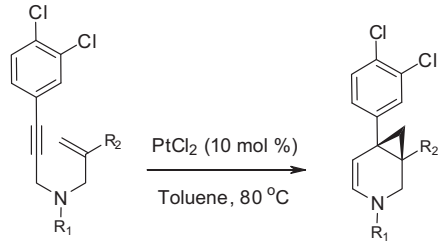
The above enynes were then subjected to cycloisomerization conditions (10 mol % $PtCl_2$, toluene, 80 °C, see Table 1) until complete disappearance of starting material was observed by HPLC. We found that substrates bearing substituted benzenesulfonamides (**1a–c**, entries 1–3) gave the cleanest reactions, with the tosylate giving the fastest reaction. Switching to carbamate protecting groups, we found that **1d** gave predominantly oxazolidinone **5** (entry 4, alkene geometry not determined). Based on previous literature reports,[11] **5** is presumably the product of *5-exo-dig* attack on the alkyne by the carbonyl oxygen followed by loss of isobutene. Interestingly, the other carbamates screened (**1e–g**, entries 5–7) gave mostly the desired enyne cycloisomerization products (i.e., 3-azabicyclo[4.1.0]heptenes), suggesting that with these substrates any competing interaction between the carbonyl oxygen and the alkyne is reversible. Reaction of the *N*-acetyl substrate **1h** led to several products (entry 8).[12] As with the carbamate series, we reasoned that this was perhaps due to interference by the amide carbonyl group. Thus, switching to the more electron withdrawing (i.e., less Lewis basic) trichloroacetyl (TCA, **1i**) and trifluoroacetyl (TFA, **1j**) protecting groups (entries 9 and 10), we found that the predominant reaction pathway was once again the desired one, although the reaction rate dropped off significantly. This was a rather general observation—the more electron withdrawing the protecting group, the slower the reaction rate, likely due to reduced electron density on the alkyne and/or alkene through inductive effects. Additionally, reduced availability of the nitrogen lone pair would presumably lead to lower migratory propensity by the propargyllic hydrogens, a proposed mechanistic step in the process.[13] Substrates in which the nitrogen lone pair was not engaged through conjugation, such as substrates **1k** (entry 11) and **3** (no protecting group on nitrogen, Scheme 2) led to decomposition.

Au(I) catalysis proved effective in accelerating the reaction, particularly for substrates such as **1j**. Thus, reaction of **1j** at room temperature in dichloromethane with 10 mol % $AuClPPh_3/AgSbF_6$ led to the formation of **4j** in less than 2 h.

In studying the effect of the substitution pattern on the alkene fragment, we were once again particularly interested in exploring substrates that would yield products easily convertible to GSK1360707. Thus, enynes **6a–d**, synthesized in analogous fashion to **1a**, were subjected to the same reaction conditions as those described in Table 1. All substrates, with the exception of **6d**,[14] proceeded to give the desired products (Table 2). Relatively electron rich olefins, such as **6a** (entry 1) gave good reaction rates (reaction completion in ~1 h), while enoate **6c** required 72 h for complete conversion (entry 3). We were also pleased to find that the free hydroxyl group in **6b** (entry 2) did not interfere with the desired cycloisomerization pathway.[15] For our purposes, we ultimately chose allyl methyl ether **1a** which was the most suitable GSK1360707 precursor.[8]

In conclusion, we have investigated the effects of nitrogen and alkene substituents on the cycloisomerization of 1,6-enynes into 3-azabicyclo[4.1.0]heptenes, with the ultimate goal of developing an

Table 2
Effect of alkene substituents[a]



6a, R_1 = *p*-Ts, R_2 = $CH_2Si(CH_3)_3$
6b, R_1 = 2-Ns, R_2 = CH_2OH
6c, R_1 = *p*-Ts, R_2 = C(O)OEt
6d, R_1 = *p*-Ts, R_2 = CH_2Cl
7a, R_1 = *p*-Ts, R_2 = $CH_2Si(CH_3)_3$
7b, R_1 = 2-Ns, R_2 = CH_2OH
7c, R_1 = *p*-Ts, R_2 = C(O)OEt
7d, R_1 = *p*-Ts, R_2 = CH_2Cl

Entry	Substrate	Time (h)	Yield[b] (%)
1	**6a**	1	96
2	**6b**	8	81
3	**6c**	72	89
4	**6d**	No reaction	N/A

[a] Reaction conditions: 10 mol % $PtCl_2$, toluene (10 ml/g **6**), 80 °C.
[b] HPLC percent area under the curve (AUC), excluding toluene peak.

efficient synthetic route to the triple reuptake inhibitor GSK1360707.[16] In general, electron-donating moieties gave faster and higher yielding reactions in both cases. A number of different substrates were well tolerated, with the exception of those where pendant functional groups (i.e., nitrogen lone pair, electron-rich carbonyl oxygen, or chloride) presumably compete irreversibly for either the catalyst or the alkyne.

3. General cycloisomerization procedure

The *N*-tethered 1,6-enyne (2 mmol, 1 equiv), toluene (10 ml per gram of substrate), and $PtCl_2$ (53 mg, 0.2 mmol, 0.1 equiv) were heated to ~80 °C in a sealed vial. The reaction progress was monitored by reverse-phase HPLC using a mixture of water and acetonitrile as mobile phase (gradient at a flow rate of 1.0 ml/min and UV detection at 220 nm). After completion, the reaction was cooled to room temperature, filtered through celite and concentrated.

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