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Chemoselective alkynylation of *N*-sulfonylamides *versus* amides and carbamates – Synthesis of tetrahydropyrazines†

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The chemoselective alkynylation of *N*-sulfonylamides *versus* amides and carbamates using TMS-EBX as an alkynylating agent leads to the formation of non-symmetrical tetrahydropyrazines from orthogonally protected diamines.

Insertion of acetylenic moieties into organic molecules is of great interest due to the specific properties of the triple bond. Transfer of an alkyne group can be realized either by nucleophilic or electrophilic alkynylation. The electrophilic alkynylation has gained interest in the last decade, due to the design of reagents, such as halogeno-alkynes, sulfone-substituted alkynes, terminal acetylenic derivatives *via in situ* oxidation or alkynyl iodonium salts (Fig. 1).[1] In order to achieve the synthesis of ynamines and ynamides,[2] iodonium salts[3] were found to be useful reagents and several methods, along with various salts, were developed since the first synthesis of ynamines using alkynyl iodonium salts by Stang *et al.*[4]

More recently, Waser *et al.* reported the α-alkynylation of activated carbonyl derivatives using trimethylsilyl ethynyl-1,2-benziodoxol-3(1*H*)-one (TMS-EBX) (**Ia**),[5] the structure of which is presented in Scheme 1, and they have also shown the synthetic potential of TIPS-EBX (**Ib**) in alkyne transfer to various aromatic heterocycles under transition metal-catalyzed conditions.[6]

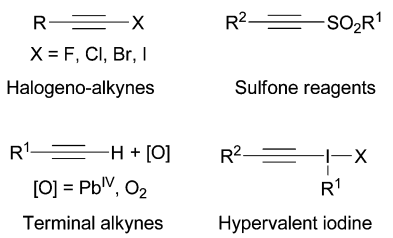
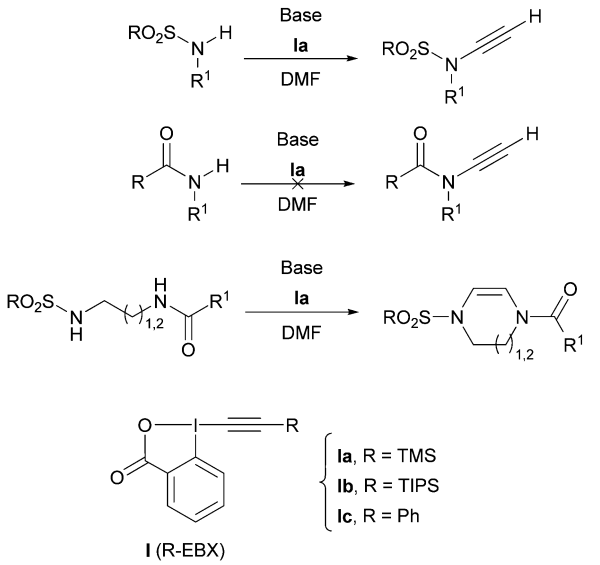


Fig. 1 Electrophilic alkynylation reagents.



Scheme 1 Chemoselective alkynylation of *N*-sulfonylamides. Synthesis of tetrahydropyrazines.

Herein, we would like to report that trimethylsilyl ethynyl-1,2-benziodoxol-3(1*H*)-one (**Ia**) can react with *N*-sulfonylamides to give the corresponding terminal ynamides but remains inactive towards amides and carbamates. By taking advantage of this chemoselectivity, tetrahydropyrazines, precursors of piperazines frequently encountered in numerous currently used drugs,[7,8] were synthesized from orthogonally protected diamines (Scheme 1).

At first, the chemoselective alkynylation of *N*-tosylamides *versus* carbamates was achieved. Compounds **1–6** were prepared and treated under basic conditions (NaH, 1 equiv.) in DMF in the presence of TMS-EBX **Ia** (1 equiv.). Under these conditions, *N*-tosylamides **1–3** were transformed into the corresponding *N*-tosylynamides **8–10** in good to excellent yield (74–93%). In contrast, carbamates **4–6** were nonreactive under these conditions. Interestingly, when diamine **7** was treated with NaH and TMS-EBX **Ia**, ynamide **11** was the only product isolated in 88% yield. The results are reported in Table 1.

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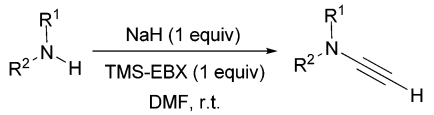
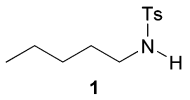
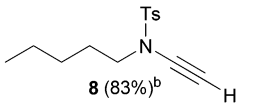
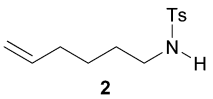
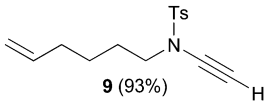
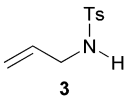
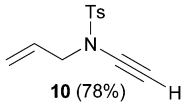
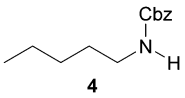
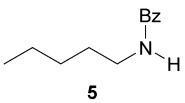
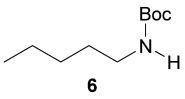
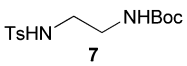
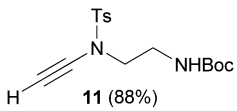
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/c3cc40529j

Table 1 Chemoselective synthesis of sulfonynamides



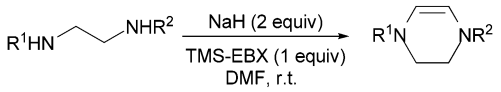
Entry	Amines	Ynamides (yield)[a]
1	 **1**	 **8** (83%)[b]
2	 **2**	 **9** (93%)
3	 **3**	 **10** (78%)
4	 **4**	—[c]
5	 **5**	—[c]
6	 **6**	—[c]
7	 **7**	 **11** (88%)

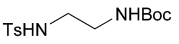
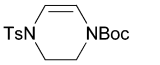
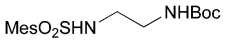
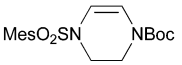
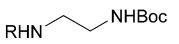
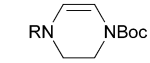
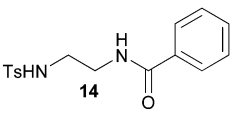
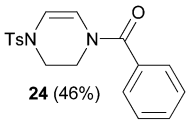
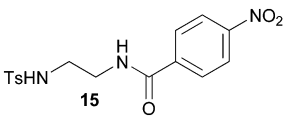
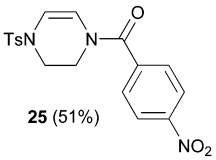
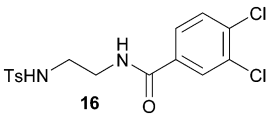
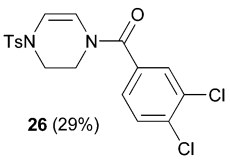
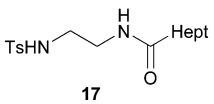
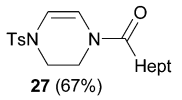
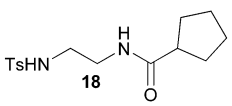
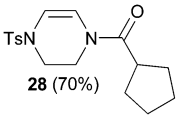
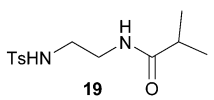
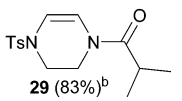
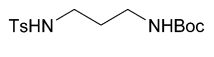
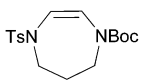
[a] Yield obtained on a 0.2 mmol scale. [b] 83% yield obtained on a 1 mmol scale. [c] No conversion.

It has been shown previously that amides can react with ynamides in the presence of a base to yield ketene *N*,*N*-acetals *via* an hydroamidation process.[9–11] To obtain similar cyclized products, compound **7** was examined and, under optimized conditions [NaH (2 equiv.) then TMS-EBX (1 equiv.) in DMF; see ESI†], compound **21** was the only product isolated with a yield of 56% (Table 2, entry 1). This product is the result of a formal 6-*endo-dig* cyclization, which is usually formed under copper-catalyzed conditions.[12,13]

Replacing the *N*-tosyl group by an *N*-mesitylene sulfonyl group as in diamine **12** did not affect the yield as the corresponding tetrahydropyrazine **22** was obtained in 51% yield (Table 2, entry 2). However, switching to a mesyl or a nosyl group decreased the yield of the cyclized products **23** and **23′** to 26% and 38% respectively (Table 2, entry 3). The influence of the second protecting group was next examined. *N*-Tosyl, *N*-benzoyl protected diamine **14** afforded the corresponding tetrahydropyrazine **24** in 46% yield (Table 2, entry 4). Substitution of the benzoyl group by one electron-withdrawing group did not affect the yield of the corresponding tetrahydropyrazine (Table 2, entry 5). However substitution of the aromatic ring with two chlorine atoms decreased the yield to 29% (Table 2, entry 6).

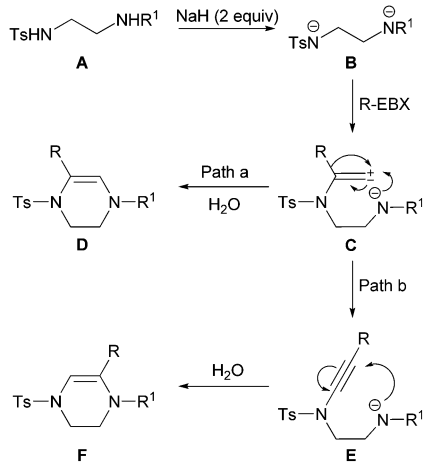
Table 2 Synthesis of tetrahydropyrazines



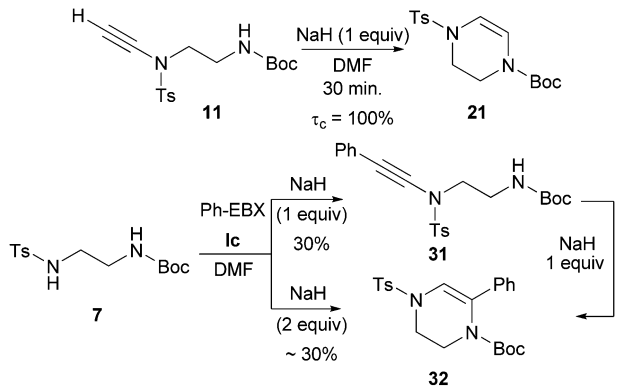
Entry	Diamines	Tetrahydropyrazines (yield)[a]
1	 **7**	 **21** (56%)
2	 **12**	 **22** (51%)
3	 **13** (R = Ms) **13'** (R = Ns)	 **23** (26%) **23'** (38%)
4	 **14**	 **24** (46%)
5	 **15**	 **25** (51%)
6	 **16**	 **26** (29%)
7	 **17**	 **27** (67%)
8	 **18**	 **28** (70%)
9	 **19**	 **29** (83%)[b]
10	 **20**	 **30** (57%)

[a] Yield obtained on a 0.2 mmol scale. [b] 81% yield obtained on a 1 mmol scale.

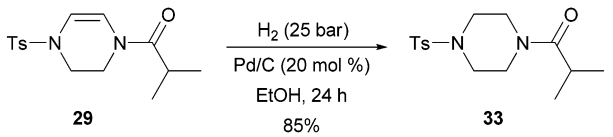
An interesting beneficial effect was observed when the *N*-benzoyl group was replaced by an alkanoyl group. Thus, when diamine **17**, substituted by an octanoyl group, was treated with **Ia**, tetrahydropyrazine **27** was isolated in a good yield of 67% (Table 2, entry 7). Similarly, cyclopentane-carboxamide **18** was transformed to **28** in 70% yield (Table 2, entry 8). The best result was obtained with the isobutyric amide **19** which was



Scheme 2 Possible pathways for the formation of tetrahydropyrazines.



Scheme 3 Mechanistic investigations.



Scheme 4 Hydrogenation of tetrahydropyrazines to piperazines.

converted to its corresponding tetrahydropyrazine **29** in 83% yield (Table 2, entry 9).

This method was also found to be suitable for the construction of seven-membered heterocycles. 1,3-Diaminopropane **20** was smoothly transformed to the corresponding tetrahydro-1,4-diazepine **30** in 57% yield (Table 2, entry 10).

On the basis of these results and precedent studies on the behaviour of ynamides and hypervalent iodine derivatives, a possible mechanism is depicted in Scheme 2. As described previously,[5] the reaction of a carbanion with TMS-EBX led to the formation of an intermediate carbene. Therefore, for bis-amide **B**, formed by treatment of diamine **A** with two equiv. of NaH, the more nucleophilic *N*-tosyl amide is supposed to react with R-EBX **I** to produce carbene **C**. Two pathways can take place; either carbene **C** can be trapped by the remaining amide to form a transient vinylic carbanion leading to **D** (Path a), or it can undergo a rearrangement to produce intermediate ynamide **E** which can produce **F** after cyclization and hydrolysis (Path b).

The discrimination between the two pathways was troublesome, as the silyl group (R = TMS) tends to be cleaved under basic conditions. However, treatment of ynamide **11** with NaH in DMF produced tetrahydropyrazine **21** with full conversion of **11**. In addition, when **7** was treated with one equivalent of NaH and then with Ph-EBX **Ic**, ynamine **31** was formed and then cyclized to tetrahydropyrazine **32** when treated with a second equivalent of NaH. It is worth noting that tetrahydropyrazine **32** was also obtained as the major product[14] when diamine **7** was treated directly with two equivalents of NaH. These results are in full agreement with Path b (Scheme 3).

Eventually, the tetrahydropyrazines can be easily transformed to the corresponding piperazines by reduction using Pd/C under an hydrogen atmosphere (25 bar) and tetrahydropyrazine **29** was indeed effectively transformed to piperazine **33** in 85% yield (Scheme 4).

In summary, ethynyl-1,2-benziodoxol-3(1*H*)-ones (R-EBX) **I** have been found to be good and chemoselective alkynylating reagents of *N*-tosyl amides. This selectivity applied to orthogonally protected diamines can be useful to synthesize non-symmetrical tetrahydropyrazines which can then be involved in the synthesis of important therapeutic agents.

Notes and references

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