Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3725–3728
Tetrahedron Letters

Expeditive synthesis of homochiral fused tri- and tetrazoles–piperazines from β-amino alcohols ☆

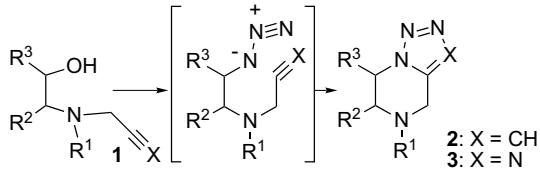
François Couty,* François Durrat and Damien Prim

SIRCOB, UMR CNRS 8086, Université de Versailles, 45, avenue des Etats-Unis, 78035 Versailles Cédex, France

Received 10 February 2004; revised 11 March 2004; accepted 16 March 2004

Abstract—*N*-Cyanomethyl and *N*-propargyl β-amino alcohols are chlorinated with $SOCl_2$ and treated with NaN_3 in DMSO. A substitution/cycloaddition process affords in good yields, with high diastereoselectivity and a regioselectivity depending on the substitution pattern of the starting amino alcohol, fused tri- and tetrazoles–piperazines. These heterocycles were further lithiated with *n*-BuLi at the benzylic position and reacted diastereoselectively with a range of electrophiles.

Synthetic procedures for the straightforward production of original heterocycles including in their framework well-established pharmacophores and using available starting material are of high interest in medicinal chemistry. Due to the emergence of combinatorial[1] chemistry and high speed parallel synthesis, such synthetic procedures are of special interest when they involve starting material that can be easily derivatized with the aim to introduce chemical diversity and that are available in enantiomerically pure form, in order to produce the target heterocycles in nonracemic form. This is the case with α-amino acids and β-amino alcohols[2] that are accessible from the chiral pool and that can be N-alkylated with a variety of substituents. We wish to describe herein the two-steps synthesis of fused tri- and tetrazoles–piperazines, respectively, **2** and **3** from N,N-disubstituted β-amino alcohols **1**, (Scheme 1) and the further diastereoselective functionalization of these heterocycles using anionic chemistry. Taking into account the frequent occurrence of triazoles, tetrazoles and piperazines in biologically active compounds,[3] as well as the scarcity in the literature of 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazine[4] and 5,6,7,8-tetrahydro-tetrazolo[1,5-*a*]pyrazine[5] cores, respectively, **2** and **3**, this methodology should be of interest for medicinal chemists.



Scheme 1. Synthesis of fused tri- and tetrazoles–piperazines from β-amino alcohols.

This synthesis uses as key step an intramolecular [2 + 3] cycloaddition between a nitrile[6] or alkyne and an azide, to give, respectively, **3** or **2**. This important reaction has already been employed as key step for the preparation of bioactive compounds.[7]

Thus, we recently reported that the chlorination ($SOCl_2$) of *N*-cyanomethyl β-amino alcohols derived from available β-amino alcohols was regio- and stereoselective and gave in high yields chlorinated amines **4**–**7**.[8] These compounds were in turn converted into 2-cyano azetidines. We found that the treatment of these chlorides with sodium azide in DMSO at 150 °C gave good yields of fused tetrazole–piperazines **8**–**12**. While chlorides **4**–**6** bearing a phenyl ring gave a single isomer, chloride **7** gave a roughly 1/1 separable mixture of regioisomers **11** and **12**. Taking into account the overall retention observed in this reaction, proved by NOE experiments performed with compounds **8** and **9**, it can be deduced that this reaction most probably involves the formation of an aziridinium intermediate **A**, which is opened regioselectively at the benzylic position, in case

Keywords: Triazoles; Tetrazoles; Organolithium.
☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.03.092
* Corresponding author. Tel.: +33-139254455; fax: +33-139254452; e-mail: couty@chimie.uvsq.fr

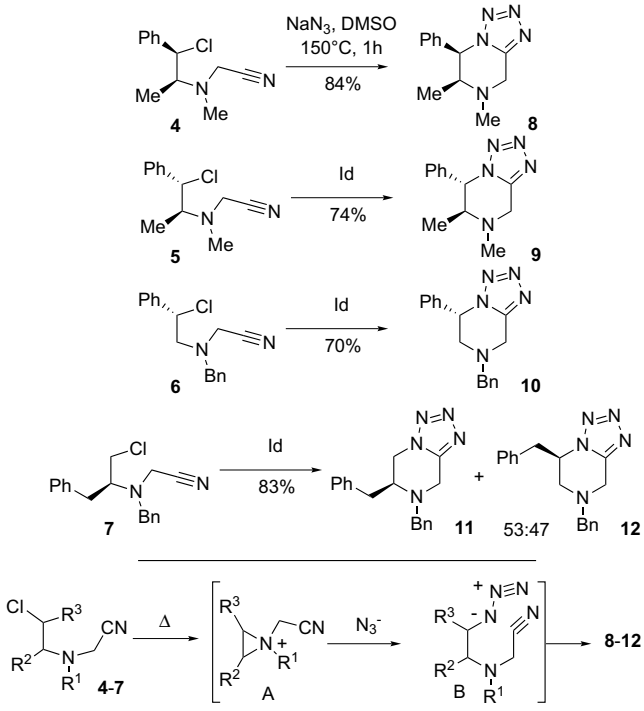
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.092

of chlorides **4**–**6** and at both positions in case of **7**, to give the corresponding azide **B** with overall retention. The latter then undergoes an intramolecular cycloaddition with the nitrile moiety (Scheme 2).

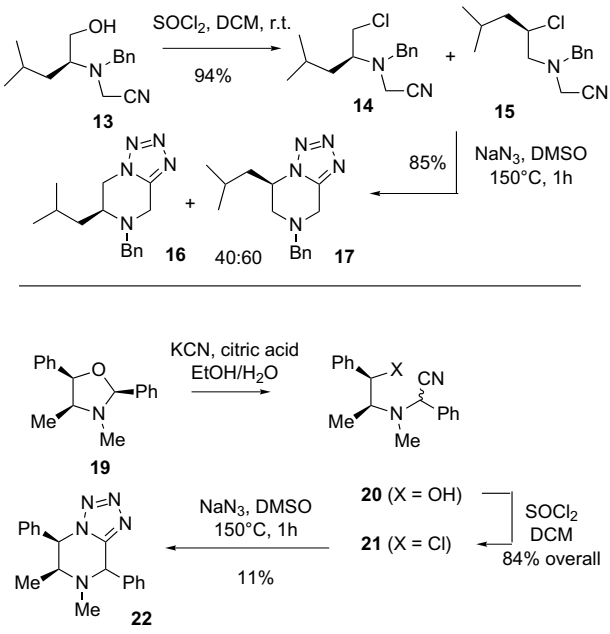
This reaction can be conducted with a mixture of isomeric chlorides. Thus, L-leucinol-derived amino alcohol **13** gave a roughly 1/1 mixture of regioisomeric chlorides **14**–**15** upon treatment with $SOCl_2$, which were reacted with sodium azide to give separable bicyclic isomers **16** and **17** in a 4/6 ratio. An attempt of substitution at the cyanomethylene moiety met however less success in this reaction. Indeed, amino alcohol **20**, resulting from the acid-catalyzed opening of oxazolidine **19**[9] in the presence of KCN was obtained as a 6/4 mixture of isomers. Chlorination gave chloride **21** showing the same diastereoisomeric ratio but the one pot substitution/cycloaddition process was accompanied in this case by extensive decomposition: from the complex mixture, only 11% yield of **22** (single isomer) could be isolated by crystallization (Scheme 3).

This methodology could be extended to the preparation of fused piperazine–triazole. In this event, (−)-ephedrine **23** was alkylated with propargyl bromide and the obtained alcohol **24** was chlorinated upon treatment with thionyl chloride. In this case, neutralization of the reaction mixture induced formation of aziridinium salts, reflecting the increased nucleophilicity of the secondary amine in this *N*-propargyl derivative, compared to the cyanomethylated analogue **4**.[10] This intramolecular alkylation could be avoided by using a simplified one pot experimental procedure: treatment of **24** with $SOCl_2$ in dichloromethane was followed by evaporation of the solvent and gave crude stable chlorhydrate **25** that was directly treated with an excess of NaN_3 in DMSO. In this case, the substitution–cycloaddition process was finished after 1 h at 110 °C, to give **26** as a single isomer whose structure was confirmed by NOE experiments (Scheme 4).

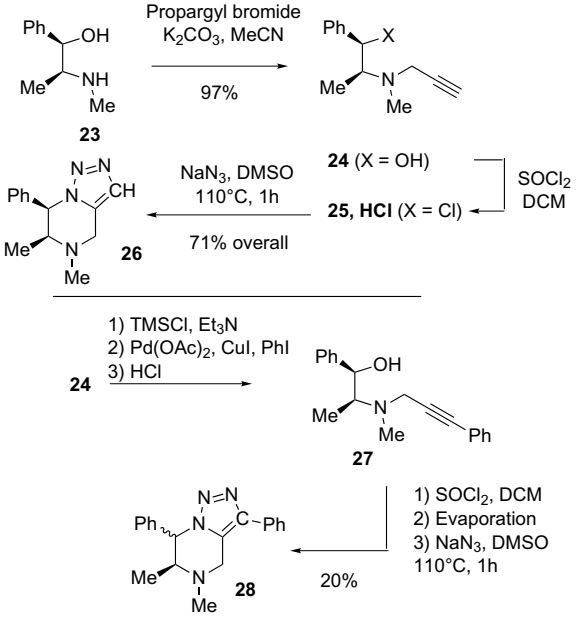
An attempt to perform this substitution–cycloaddition process with phenyl-substituted alkyne **27**, obtained from **24** using palladium-catalyzed chemistry, was however deceiving. In this case unidentified by-products



Scheme 2. An intermediate aziridinium ion accounts for the regioselectivity of the process.



Scheme 3. Further examples of fused tetrazole–piperazines syntheses.



Scheme 4. Synthesis of fused triazole–piperazines.

were formed, and the expected triazole was obtained with a low yield as a near 1/1 mixture of isomers at the phenyl substituted stereocentre, indicating that direct substitution of the azide anion on the chlorinated centre may be here a competing process. This highlights the fact that subtle modifications of the substituents on the nitrogen atom can profoundly influence the stereochemical course of this reaction.

The further functionalization of these heterocycles was also studied. We found that both bicyclic tetrazole **8** and triazole **26** were cleanly metallated upon reaction with *n*-butyllithium at −78 °C in THF at the benzylic position, producing the corresponding chiral benzyllithium reagents as deep red solutions. Quench of these benzyllithiums with different electrophiles afforded the corresponding substituted derivatives at the benzylic position. The results of these experiments are gathered in Table 1.

Some general comments should be made concerning this lithiation that considerably extends the chemical diversity attainable using this synthetic methodology. First, while α-lithio triazoles reagents are well-documented and useful synthetic tools,[11] α-lithio tetrazoles are much less reported[12] and this work is, to our knowledge, the first report concerning the reactivity of chiral non racemic α-lithio tetrazoles. Secondly, the regioselectivity of this metallation is total: no competitive lithiation takes place on the methylene moiety.[13] Finally, the stability of these anions is surprising: in no case, even at 0 °C, have we been able to detect products resulting from a β-elimination.[14]

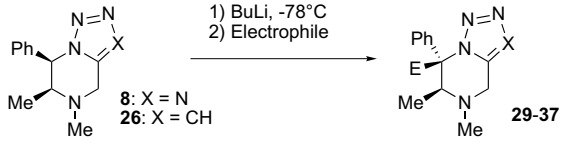
Deuteration experiments (entries 1 and 5) revealed that lithiation and equilibration of the benzylic lithium derivatives of both heterocycles occurs within experimental timescale. Considering the stereochemistries in **29** and **34**, the more stable lithium organometallic probably display a *trans* relationship between the phenyl and adjacent methyl group since α-heterosubstituted benzyllithium reagents are reported to be protonated or deuterated with retention of configuration.[15] These benzyllithium reagents could be alkylated stereoselectively with different halides (entries 4,7 and 8). Reaction with methyl iodide unexpectedly gave compound **32** as a byproduct incorporating a butyl group: this can be explained by a competitive metal/halogen exchange between methyl iodide and butyllithium. The high stereoselectivities observed with BuI, BnBr and acetone probably reflect the high rate of equilibration of the anion compared to the kinetic of the S_E2 process. On the other hand, TMSCl and MeOTf reacted more sluggishly and with poor yield and selectivities (entries 4 and 8). Given the possibility of both $S_E2$inv and $S_E2$ret mechanisms depending on the nature of the electrophile,[16] the intimate mechanism of this reaction merits further studies.

In summary, we have disclosed an access to nonracemic fused tri- and tetrazoles–piperazines using very simple experimental procedures and readily available starting material, as well as the further diastereoselective functionalization of these heterocycles using anionic chemistry. Further work is in progress in our group in order to extend the scope of this one pot substitution–cycloaddition process to other new kinds of heterocycles.

Supplementary material

Representative experimental procedures for the preparation of **8**, **26** and **35**.

Table 1. Lithiation experiment of **8** and **26**



Entry[a]	Substrate	E^+	Product(s)	De (%)	Yield (%)
1[b]	**26**	CD_3OD	**29**: X = CH, E = D	80	95
2	**26**	MeOH	**30**: X = CH, E = H	80	95
3	**26**	MeI	**31**: X = CH, E = Me	80	41
			32: X = CH, E = Bu	>95	32
4	**26**	TMSCl	**33**: X = CH, E = TMS	15[c]	48
5	**8**	CD_3OD	**34**: X = N, E = D	33	92
6	**8**	$(Me)_2CO$	**35**: X = N, E = CMe_2OH	>95	79
7	**8**	BnBr	**36**: X = N, E = Bn	>95	75
8	**8**	MeOTf	**37**: X = N, E = Me	5[c]	50
9[d]	**8**	$(Ph)_2CO$	—	—	—

[a] Conditions otherwise stated: *n*-BuLi (2 equiv), THF, −78 °C, 15 min then E^+ (3 equiv), −78 °C, 30 min.
[b] Shortened (5 min) or protracted (30 min) reaction times with *n*-BuLi gave similar results.
[c] The relative stereochemistry of the major isomer was not determined.
[d] No reaction occurred at −78 °C. The reaction was quenched at 0 °C after 1 h and the major product in the reaction mixture was **9**.

References and notes

1. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
2. For recent examples using β-amino alcohols in combinatorial chemistry see: (a) Jefferson, E. A.; Arakawa, S.; Blyn, L. B.; Miyaji, A.; Osgood, S. A.; Ranken, R.; Risen, L. M.; Swaayse, E. E. *J. Med. Chem.* **2002**, *45*, 3430–3439; (b) Wipf, P.; Wang, X. *J. Comb. Chem.* **2002**, *4*, 656–660; (c) Conde-Frieboes, K.; Schjeltved, R. K.; Breinholt, J. *J. Org. Chem.* **2002**, *67*, 8952–8957.
3. Lednicer, D. *Strategies for Organic Drugs Synthesis and Design*; John Wiley and Sons, 1998.
4. For a recent example of biologically active 1,2,3-triazolo[1,5-*a*]quinoxaline, see: Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Betti, L.; Giannaccini, G.; Trincavelli, M. L. *Eur. J. Med. Chem.* **2002**, *37*, 565–571.
5. For a recent example of synthesis of fused tetrazole–ketopiperazines, see: Nixey, T.; Kelly, M.; Hulme, C. *Tetrahedron Lett.* **2000**, *41*, 8729–8733.
6. For a recent theoretical study, see: Himo, F.; Demko, Z. P.; Noodleman, L. *J. Org. Chem.* **2003**, *68*, 9076–9080.
7. For some examples, see: (a) Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043–2053; (b) Davis, B. G.; Hull, A.; Smith, C.; Wash, R. J.; Watson, A. A.; Winkler, D. A.; Griffith, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2947–2960.
8. Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2002**, *13*, 297–302.
9. Neelakantan, L. *J. Org. Chem.* **1971**, *36*, 2253–2256.
10. This may be ascribed to an $nN \rightarrow \sigma^{*}C\text{–}CN$ overlap (anomeric effect), which deactivates the lone pair on the nitrogen in *N*-cyanomethyl derivatives.
11. Katritzky, A. R.; Huang, Z.; Fang, Y.; Prakash, I. *J. Org. Chem.* **1999**, *64*, 2124–2126.
12. We found a single example: Moody, C. J.; Rees, C. W.; Young, R. G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 323–327.
13. For a recent example reporting the lithiation α to the carbon of a tetrazole heterocycle, see: Yang, M. G.; Modi, D. P.; Wexler, R. R.; Olson, R. E. *Tetrahedron Lett.* **2004**, *45*, 111–112.
14. *N*-Boc α-lithio piperazines are known to undergo β-elimination: Garrido, F.; Mann, A.; Wermuth, C.-G. *Tetrahedron Lett.* **1997**, *38*, 63–64.
15. Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561–11570.
16. Clayden, J. Organolithium: Selectivity for Synthesis In *Tetrahedron Organic Series*; 2002; pp 241–271.