ORGANIC LETTERS

2011
Vol. 13, No. 19
5044–5047

Copper-Free Intramolecular Alkyne–Azide Cycloadditions Leading to Seven-Membered Heterocycles

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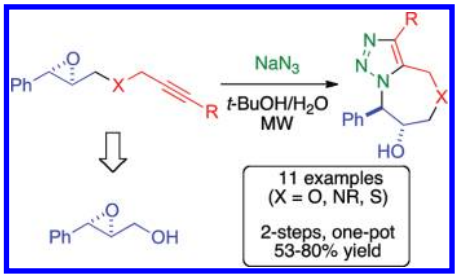
Received July 12, 2011

ABSTRACT



Treatment of alk-2-ynyl derivatives of enantiopure phenylglycidol with NaN_3 triggers a cascade reaction consisting of stereospecific and regioselective epoxide ring opening followed by intramolecular azide–alkyne cycloaddition under strictly metal-free conditions. This simple one-pot procedure allows a fast buildup of molecular complexity, generating a wide array of triazolooxazepinols, triazolodiazepinols, and triazolothiazepinols.

The construction of triazoles by azide–alkyne cycloaddition (AAC) has long been known,[1] but it was not until the independent discovery by the groups of Meldal[2] and Sharpless[3] that copper(I) catalyzed the process that it became a useful tool for synthetic chemists. Indeed, several catalysts have been developed that not only stabilize the Cu(I) species but also accelerate the global catalytic process,[4] which has allowed application of this transformation in fields as diverse as biotechnology and materials science.[5]

For biological applications, the cytotoxicity of copper could represent an important drawback[6] and, in fact, impressive efforts have been devoted to developing copper-free protocols that have even enabled the performance of these reactions in vivo.[7] While for intermolecular processes the strain-induced increase in reactivity of the alkyne component has evolved into a most practical approach to copper-free alkyne azide cyloadditions,[8] intramolecular

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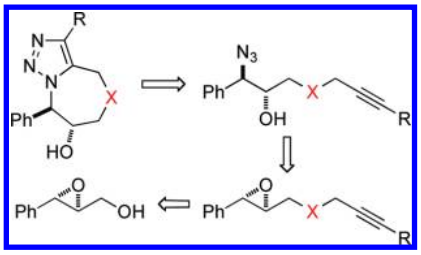
10.1021/ol201869y
Published on Web 09/02/2011

alkyne–azide cycloadditions can take place under mild conditions in the absence of copper thanks to favorable entropy effects on the corresponding transition states.[9]

Scheme 1. Aims of the Present Work



Herein, we report that enantiopure compounds involving triazole rings fused to seven-membered heterocycles (oxepanes, thiepanes, and azepanes) can be easily obtained from the corresponding propargyl derivatives (ethers, thioethers, and amines) of phenylglycidol in a two-step, one-pot operation, which is not mediated by any metallic source (Scheme 1). Despite the potential interest of these heterocyclic systems in medicinal chemistry,[10] arising from its close structural similarity with benzodiazepine drugs such as Triazolam, Alprazolam (Trankimazin, Xanax), and Estazolam (Figure 1), synthetic methods for their preparation are scarce,[9c,f,10b,11] and all chiral approaches to these compounds rely on the construction of the molecules on carbohydrate educts.[12]

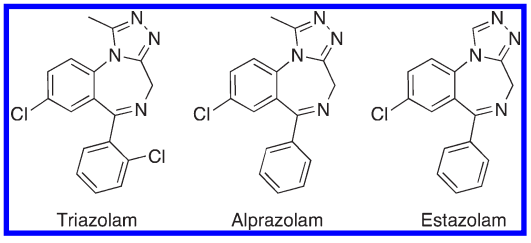
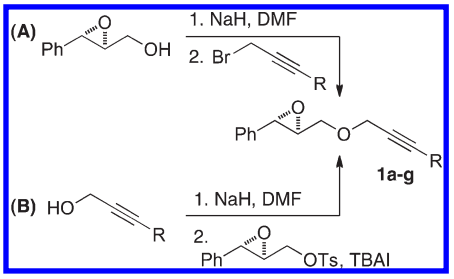


Figure 1. Benzodiazepine drugs involving triazole substructures.

For the preparation of oxepane-type products, propargyl ethers of phenylglycidol (**1a**–**g**) were prepared by two different strategies: deprotonation of phenylglycidol followed by substitution on the corresponding propargyl halide (Scheme 2, route A) or attack of a propargyl alkoxide to the tosylate ester of phenylglycidol (Scheme 2, route B).

Scheme 2. Preparation of Phenyglycidyl Propargyl Ethers **1a**–**g**



The results obtained in the preparation of these ethers are summarized in Table 1.

Table 1. Preparation of Phenyglycidyl Propargyl Ethers **1a**–**g**

entry	R	method	yield [%]	product
1	H	A	86	**1a**
2	Me	A	80	**1b**
3	Ph	A	78	**1c**
4	2-naphthyl	A	80	**1d**
5	*n*-pent	A	85	**1e**
6	CH_2OPMB	B	53	**1f**
7	CH_2OH	B[a]	74	**1g**

[a] Obtained by deprotection of **1f** with DDQ.

With ethers **1a**–**g** in hand, the stage was set to search for the optimal reaction conditions for the planned cascade process, which was carried out with **1a** as the model substrate. At this point, it is worth mentioning that since the very beginning it became apparent that the kinetics governing the two consecutive reactions rendered isolation of the intermediate azido alcohol **2a** a hopeless task. Thus, no reaction conditions could be found where **2a** could be formed without concomitant generation of significant amounts of the cyclization product **3a**.[13] Nevertheless, this only played to our advantage, since fine-tuning of reaction conditions for the two consecutive processes would allow the transformation to be carried out in a one-pot manner, thus avoiding the isolation of potentially dangerous organic azides.

The first efforts toward optimization focused on the solvent. Here, the choice was quite narrow since we wanted

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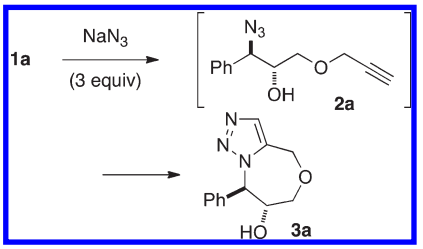
(13) Throughout the rest of the work no intermediates were isolated other than **2a**. For the complete characterization of **2a**, see Supporting Information.

the reaction to take place under homogeneous conditions. Thus, only MeCN, DMF, and *t*-BuOH/H_2O were found to fulfill the above condition and were subsequently tested (Table 2). Very disappointing results were recorded with polar aprotic solvents (entries 1 and 2) under both purely thermal and microwave promoted reaction conditions. Even the attempt of promoting epoxide ring opening in acetonitrile with Lewis acid catalysis ($LiClO_4$)[14] led to impractical reaction mixtures after prolonged reaction times (entry 3).

On the contrary, reaction in *t*-BuOH/H_2O occurred under mild conditions to afford **3a**, but it required 18 h at 100 °C for complete conversion (entry 4). Interestingly, reaction times could be significantly reduced by performing the cascade process under microwave irradiation (entry 5). The reaction conditions employed in this experiment (3 equiv of NaN_3 in *t*-BuOH/H_2O under MW irradiation) were considered optimal and were used for the rest of this study.

Table 2. Optimization of the Reaction Conditions for the Cascade Process Leading to **3a**



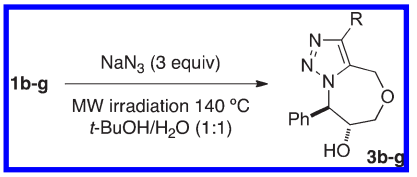
entry	solvent	temp [°C]	time [h]	**1a/2a/3a**
1	DMF	95	0.5	100:0:0 (MW)
2	MeCN	100	12	100:0:0
3[a]	MeCN	75	24	13:46:41
4	*t*-BuOH/H_2O	100	18	0:0:100
5[b]	*t*-BuOH/H_2O	100	3	0:0:100 (MW)

[a] Reaction performed with NaN_3 (2.0 equiv) and $LiClO_4$ (1.2 equiv). [b] With the optimal conditions, **3a** was isolated in 70% isolated yield.

With these optimized conditions the scope of the reaction with internal alkynes was investigated. However, although the reaction proved quite general with respect to substrate modification at the alkyne fragment, higher temperatures were required to achieve full conversion of internal alkynes in reasonable reaction times. In fact, this parameter had to be fine-tuned for each substrate to preclude formation of decomposition products. The best conditions found for the two-step azide substitution−AAC of substrates **1b**−**g** are outlined in Table 3.

As can be seen, good yields were obtained in all cases for the considered two-step process (yields per individual step are in the 80−90% range). It is worth mentioning that all products obtained in the course of this study were formed

Table 3. Preparation of (7*R*,8*R*)-8-Phenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo[5,1-*c*][1,4]oxazepin-7-ols **3b**−**g** by Cascade Epoxide Ring Opening plus AAC Reaction from Phenylglycidyl Propargyl Ethers **1b**−**g**



entry	R	time [h]	yield [%]	product
1	Me	2.5	60	**3b**
2	Ph	1.5	80	**3c**
3	1-naphthyl	2	68	**3d**
4	*n*-pentyl	1.5	70	**3e**
5	CH_2OPMB	1.5	63	**3f**
6	CH_2OH	2	60	**3g**

as single diastereoisomers having the *trans* configuration, as indicated by NMR analysis (the diagnostic methine proton α to phenyl appeared in all cases as a doublet at *ca.* 6.5 ppm with J = 4.6−4.7 Hz).[15] This stereochemical assignment could be confirmed by X-ray diffraction in the case of **3f** (Figure 2). Given the very close similarity between the relevant parts of the NMR spectra of **3a**−**g** (see above), the *trans* configuration was confirmed for the rest of the series.

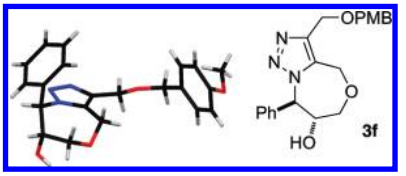


Figure 2. X-ray structure of (7*R*,8*R*)-**3f**.

The glycidyl propargylamines and thioethers **4a**−**d** required for the preparation of the analogous azepane and thiepane systems **5a**−**d** (Table 4) were easily prepared from phenylglycidyl *p*-toluenesulfonate (see Supporting Information). As expected, substrates **4a**−**d** underwent regioselective epoxide ring opening with concomitant AAC to afford **5a**−**d** when submitted to microwave heating with 3 equiv of NaN_3, as shown in Table 4.

As already noted for the formation of **3a**−**g**, the cascade process triggered by the ring opening of **4a**−**d** with azide took place in a stereospecific manner involving inversion at the benzylic carbon. Thus, reaction products **5a**−**d** were again obtained as single *trans* diastereomers according to NMR analysis. For the preparation of drug-like

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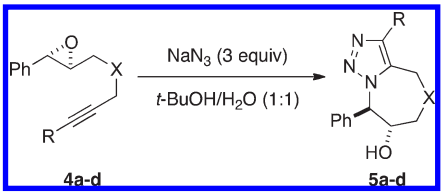
Table 4. Preparation of [1,2,3]Triazolo[5,1-*c*][1,4]diazepin-7-ols and [1,2,3]Triazolo[5,1-*c*][1,4]thiazepin-7-ols **5a**–**d** by Cascade Epoxide Ring Opening plus AAC Reaction from Derivatives **4a**–**d**



entry	R	X	temp [°C]	*t* [h]	yield [%]	product
1	H	NH	110	2.5	60	**5a**
2	H	NBn	130	3	70	**5b**
3	H	NBu	130	3	85	**5c**
4	Ph	S	140	1.5	53	**5d**

[1,2,3]triazolo[5,1-*c*][1,4]diazepin-7-ols, such as **5b**–**c**, the unsubstituted N–H derivative **5a** could be considered as a convenient relay; however, purification of this compound is problematic (see Supporting Information) and, although crude **5a** has been successfully converted into **5b** by alkylation, it is advisible to prepare derivatives **5** using phenylglycidyl *p*-toluenesulfonate as the source of diversity (see Scheme 2, route B).

(16) Patent pending.

In conclusion, a straightforward procedure for the generation in enantiopure form of bicyclic systems featuring a triazole ring fused to a seven-membered heterocycle (oxepane, azepane, or thiepane) through a cascade process involving regioselective and stereospecific epoxide ring opening with azide plus a copper-free intramolecular AAC reaction has been developed.[16] The highly modular character of the resulting bicyclic systems, which offer up to four readily fine-tunable points of diversity, together with its potential as enantiopure benzodiazepine analogs, provides these substances with additional interest.

Acknowledgment. This work was funded by MICINN (Grant CTQ2008-00947/BQU), DIUE (Grant 2009SGR623), Consolider Ingenio 2010 (Grant CSD2006-0003), and the ICIQ Foundation. The authors gratefully acknowledge M. Martínez Belmonte, Eduardo Escudero-Adán, and J. Benet-Buchholz (X-ray diffraction unit, ICIQ) as well as G. Gómez Castresana and G. González (NMR spectroscopy unit, ICIQ) for their invaluable help with X-ray diffraction and NMR techniques.

Supporting Information Available. Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. X-ray crystalographic data (CIF) for **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.