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Intramolecular Azide–Alkyne Cycloaddition for the Fast Assembly of Structurally Diverse, Tricyclic 1,2,3-Triazoles

Ana I. Oliva,[†] Ute Christmann,[†] Daniel Font,[†] Félix Cuevas,[†] Pablo Ballester,[‡] Helmut Buschmann,[#] Antoni Torrens,[#] Susana Yenes,[#] and Miquel A. Pericàs*[,§]

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans, 16, 43007 Tarragona, Spain, Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain, ICREA and Laboratorios Dr. Esteve, S.A., Av. Mare de Deu de Montserrat, 221, 08041 Barcelona, Spain

mapericas@iciq.es

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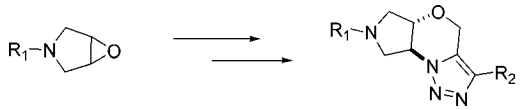
ABSTRACT



The synthesis of novel tricyclic 1,2,3-triazoles starting from cyclic epoxides via the sequential azidolysis, propargylation and 1,3-dipolar cycloaddition is described. Derivatization by *N*-arylation reaction and the synthesis of enantiomerically pure compounds is also reported. Some of these compounds exhibit significant affinity for the sigma-1 receptor.

In recent years, the 1,3-dipolar cycloaddition between azides and alkynes has witnessed a renewed interest since the introduction by Sharpless of the Click Chemistry concept.[1] In most cases, the 1,2,3-triazole system resulting from the cycloaddition represents an almost universal ligation element allowing the fast connection of properly functionalized components of very diverse natures with quite different functions/activities.[2] In addition, the 1,2,3-triazole unit can itself exhibit interesting properties, either catalytic or pharmacological, among others.[3]

The versatility of this cycloaddition has driven the development of tandem processes involving it as the key step, as a ready access to molecular diversity.[4] Among these multicomponent constructions, the combination of epoxide ring-opening with azide, *O*-propargylation and intramolecular azide−alkyne cycloaddition appears as a most promising alternative for the fast assembly of drug-like, tricyclic 1,2,3-triazoles. However, either the fact that the involved dipolar cycloaddition does not adjust to the structural requirements of the click chemistry paradigm or the belief that the trans arrangement in the cycloaddition substrate would play a negative role on the cycloaddition process have hampered the exploration of this possibility until now.

We report herein that cyclic epoxides, when submitted to sequential azidolysis plus propargylation, lead to stereodefined azidoalkynes that readily undergo purely thermal 1,3-dipolar cycloaddition leading to tricyclic [1,2,3]triazolo[1,5-*d*][1,4]oxazines. The introduction of structural diversity at two key points in these tricyclic structures is also demon-

[†] ICIQ.
[‡] ICREA and ICIQ.
[#] Laboratorios Dr. Esteve, S. A.
[§] ICIQ and UB.

(1) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Rostovsev, V. V.; Gree, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(2) (a) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (b) Lutz, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018.

(3) (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (b) Whiting, M.; Mudoon, J.; Lin, Y. C.; Silverman, S. M.; Lindstrom, W.; Olson, A. J.; Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 1435. (c) Luo, S.; Xu, H.; Mi, X.; Li, J.; Zheng, X.; Cheng, J. P. *J. Org. Chem.* **2006**, *71*, 9244. (d) Detz, R. J.; Arevalo, S.; De Gelder, R.; van Leeuwen, P. W. N. M.; Hiemstra, H.; Reek, J. N. H.; van Maarseven, J. H. *Org. Lett.* **2006**, *8*, 3227.

(4) (a) Thomas, A. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1881. (b) Khanetskyy, B.; Dallinger, D.; Kappe, C. O. *J. Comb. Chem.* **2004**, *6*, 884. (c) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439. (d) Gracias, V.; Darczak, D.; Gasiecki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, *46*, 9053.

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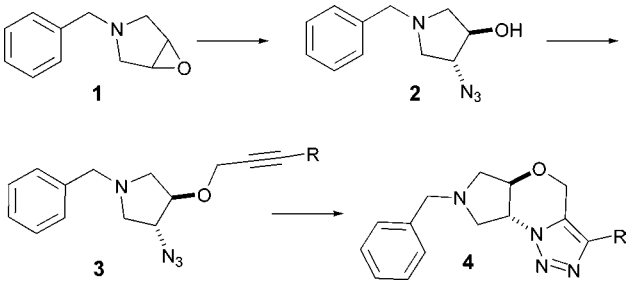
strated, and access to enantiopure products is secured by catalytic desymmetrization of the starting epoxide with azide delivering reagents.

Our strategy to prepare the tricyclic compounds starting from benzylpyrroline epoxide **1** is outlined in Scheme 1. The

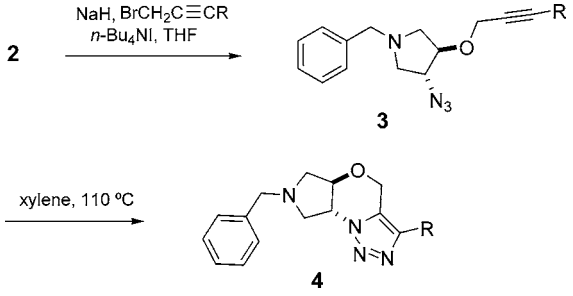
Scheme 1. Synthetic Sequence



combination of the opening reaction with NaN_3, alkylation of the resulting alcohol with propargyl bromides and the subsequent intramolecular cycloaddition of the alkynyl-azido compound afforded the tricyclic triazoles as racemic mixture of trans-fused compounds **4**.

Thus, the reaction of the epoxide **1** with NaN_3 in the presence of $LiClO_4$ in acetonitrile at reflux conditions[5] afforded the racemic *trans*-azidoalcohol **2** in 90% yield. The alkylation of **2** with different propargyl bromides with NaH as base and tetrabutylammonium iodide as catalyst in THF, gave the alkynyl-azido compounds **3** in moderate to excellent yields (Table 1).

Table 1. Synthesis of Tricyclic Triazole Derivatives

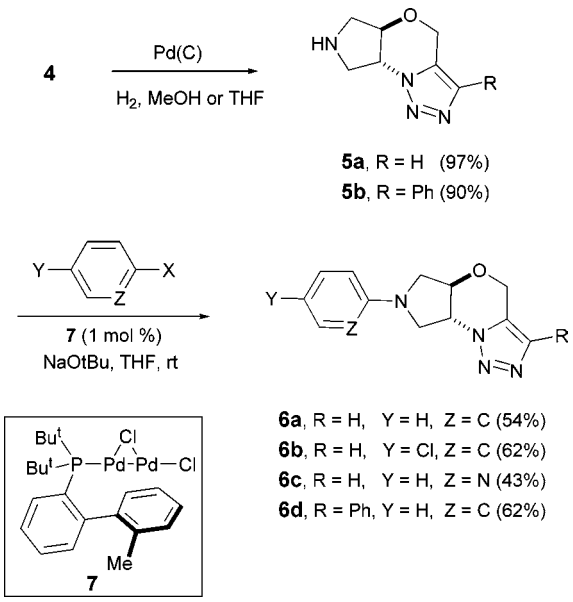


entry	R	**3** (yield, %)	**4** (yield, %)
1	H	**3a** (99)	**4a** (87)
2	Me	**3b** (77)	**4b** (93)
3	Et	**3c** (90)	**4c** (79)
4	Ph	**3d** (84)	**4d** (85)
5	2-F-C_6H_4	**3e** (50)	**4e** (66)
6	3-F-C_6H_4	**3f** (47)	**4f** (85)
7	4-Cl-C_6H_4	**3g** (61)	**4g** (77)
8	4-CF_3-C_6H_4	**3h** (35)	**4h** (86)

The intramolecular azide−alkyne cycloaddition was performed in good yields upon heating in toluene or xylene to afford compounds **4** (Table 1). As anticipated, only 1,5-regioisomers were obtained. The cycloaddition was also attempted using copper-catalyzed conditions with unsubstituted propargyl compound **3a**, but no adduct was formed probably due to geometry restrictions in the formation of the 1,4-regioisomer.

To increase structural diversity in the new compounds prepared, we thought that the nitrogen of the pyrroline subunit was good to derivatize. Thus, we studied the palladium catalyzed *N*-arylation reaction with aryl halides (Scheme 2).[6] The hydrogenolysis of compounds **4** with Pd/C

Scheme 2. Debenzylation of **4** and Derivatization by the *N*-Arylation Reaction



in methanol or THF afforded the secondary amine in good yields. For the *N*-arylation reaction, we found that 1 mol % of precatalyst **7** was able to mediate the coupling between **5** and different aryl halides in presence of NaO*t*Bu in THF at room temperature in good yields.[7]

Moreover, this novel synthetic approach can be applied to the synthesis of enantiopure tricyclic triazoles. For the asymmetric version, we used the enantiomerically pure Boc-protected azido alcohol **8** as key intermediate. This intermediate can be prepared by asymmetric ring opening of the *N*-trifluoroacetamide pyrroline epoxide with $TMSN_3$ catalyzed by the chiral (salen)Cr(III) complex (*R*,*R*)-**L**, and subsequently *N*-Boc protection according to described procedures (Table 2).[8] In our hands, the azido alcohol was obtained in 94% ee from the corresponding *N*-trifluoro-

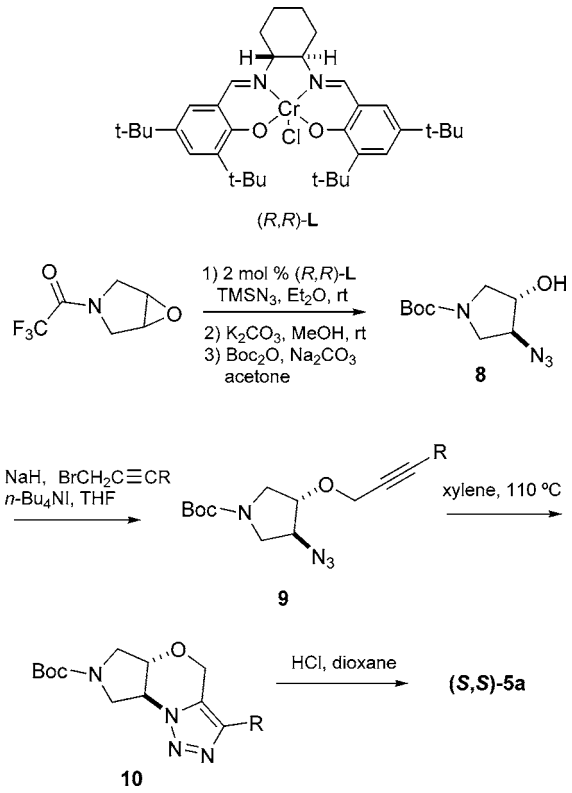
(5) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221.

(6) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144. (b) Wentland, M. P.; Xu, G.; Cioffi, C. L.; Ye, Y.; Duan, W.; Cohen, D. J.; Colasurdo, A. M.; Bidlack, J. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 183. (c) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(7) (a) Christmann, U.; Vilar, R.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **2004**, 1294. (b) Christmann, U.; Pantazis, D. A.; Benet-Buchholz, J.; McGrady, J.; Maseras, F.; Vilar, R. *J. Am. Chem. Soc.* **2006**, *128*, 6376.

(8) (a) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (b) Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197.

Table 2. Synthesis of Enantiomerically Pure Tricyclic Triazoles



entry	R	**9** (yield, %)	**10** (yield, %)
1	H	**9a** (92)	**10a** (96)
2	Me	**9b** (96)	**10b** (47)
3	Ph	**9c** (80)	**10c** (57)
4	3-F-C_6H_4	**9d** (91)	**10d** (86)

acetamide epoxide. The alkylation of **8** in the conditions described above and the intramolecular cycloaddition of the alkyne−azido compounds gave a variety of enantiopure triazoles **10** in good yields (Table 2 and Supporting Information). Finally, the deprotection of the *N*-Boc group and the subsequent *N*-derivatization will provide enantiomerically pure compounds. In the case of **10a**, the deprotection of the Boc group afforded the enantiopure amino derivative **5a** as dihydrochloride salt form, where the (*S*,*S*) configuration of the fused rings was confirmed by X-ray crystallographic analysis (Figure 1).

Quite interestingly, this strategy to access enantiopure tricyclic triazoles could be applied to other azido alcohols prepared by desymmetrization of the corresponding epoxides.

Representative compounds from the triazole library were tested in a wide biological screening against 160 receptors. These results revealed that some of the novel tricyclic compounds prepared exhibit high affinity and selectivity for the sigma-1 receptor. The sigma-1 receptor is of great interest in pharmacology in view of its possible physiological role in processes related to analgesia, anxiety, addiction, amnesia, and depression among others.[9] In addition, some preliminary structure−activity relationships (SARs) were found. Tricyclic

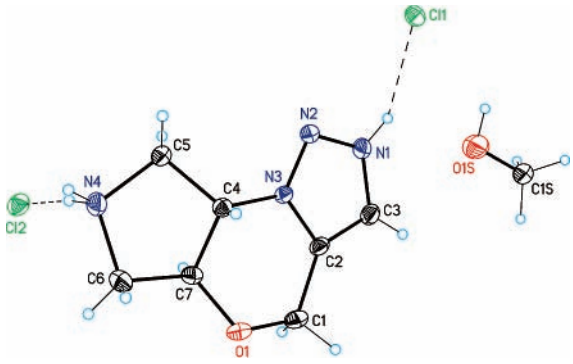


Figure 1. X-ray structure of **(*S*,*S*)-5a** (2HCl).

compounds **4** bearing a benzyl-substituted pyrroline showed activity for sigma-1, and interestingly, the affinity increased when R_2 is an aryl group (Table 3). Compound **4f**, wherein

Table 3. Affinity for the Sigma-1 Receptor

compound	Ki (nM)	% displacement (10^{-6} M)
4a		<50
4b	>1000	
4c	375 ± 1.6	
4d	26.9 ± 4.4	
4e	27.4 ± 4.9	
4f	15.8 ± 0.3	
4g		87
4h	31.3 ± 8.7	

R_2 is a *meta*-fluorine-substituted aryl, had the highest affinity (Ki 15.8 ± 0.3 nM).

In summary, we have developed a straightforward preparation of new structurally diverse tricyclic 1,2,3-triazoles based on a sequential epoxide ring-opening with azide, *O*-propargylation and intramolecular azide−alkyne cycloaddition. Furthermore, we have described the derivatization of these compounds by an *N*-arylation reaction and the synthesis of enantiomerically pure analogues. Preliminary screening results indicated that some of these compounds exhibited a high affinity for the sigma-1 receptor. More detailed SAR studies and the biological evaluation of the enantiomerically pure compounds are underway in our laboratories.

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Supporting Information Available: Detailed description of experimental procedures, ^{1}H and ^{13}C NMR spectra of the compounds, and X-ray crystalographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL800291T

(9) (a) Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; De Costa, B.; Rice, K. C. *Pharmacol. Rev.* **1990**, *42*, 355. (b) Bowen, W. D. *Pharm. Acta Helv.* **2000**, *74*, 211.