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A new modular and flexible approach to [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines

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Abstract—A new synthetic route for the access to [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines and other derivatives is described. This strategy is based on the cycloaddition of 2-oxoalkylidenephosphoranes to *o*-functionalized aryl azides followed by the reaction of the corresponding triazole intermediate with amines. This new approach presents unique properties such as regioselectivity, modularity, mild reaction conditions, and high yields.
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Among the drugs used in the treatment of central nervous system (CNS) disorders, 1,4-benzodiazepines have occupied a prominent place during the last 40 years.[1] Consequently, elegant and practical syntheses of these heterocyclic systems have been developed.[2] A simple modification of the benzodiazepine core consists of the annelation of a new heterocyclic moiety to the benzodiazepine framework.[3] *Alprazolam* (**A**) and *Estazolam* (**B**) belong to this family of compounds which possesses a 1,2,4-triazole ring fused to the 1,2 position of the diazepine (see Fig. 1). Both are common anxiolytic agents and have found both clinical and commercial success.[4]

In this context, we directed our attention to the synthesis of [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines (**C** in Fig. 1).

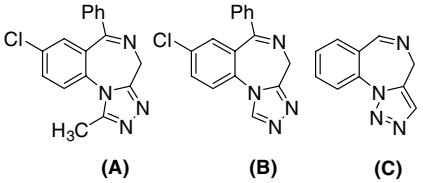

Figure 1. *Alprazolam* (**A**), *Estazolam* (**B**) and structure of 4*H*-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine (**C**).

Keywords: 1,2,3-Triazole; Ketophosphorane; *o*-Functionalized aryl azide; Bis-electrophile.
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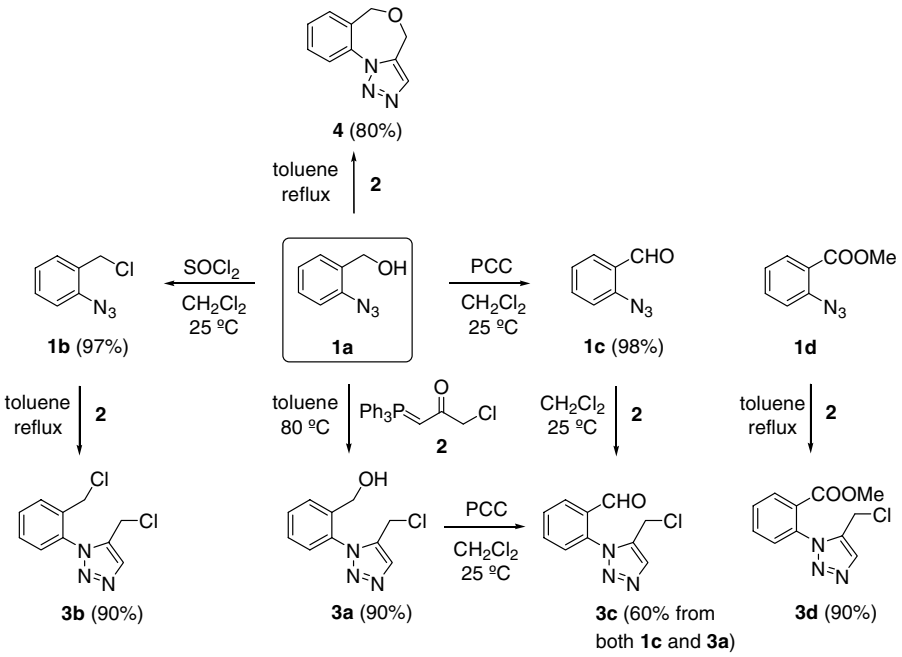
Several approaches to this type of compounds have been described previously in the literature, all of them based on inter/intramolecular cycloadditions of aryl azides to alkenes or acetylenes (Huisgen dipolar cycloaddition) to generate the triazole ring.[5] In spite of its popularity, the Huisgen approach presents some disadvantages, such as the high activation energies of these cycloadditions, which are very slow even at elevated temperatures, and the lack of regioselectivity when unsymmetrical dipolarophiles are used.[6] Recently, Sharpless and others demonstrated that these processes are catalyzed by Cu(I)[7] or Ru(II)[8] with high levels of regioselection. Surprisingly, alternative synthetic routes for the preparation of the tricyclic structures **C** have been rarely pursued.

Herein, we disclose a new synthetic strategy for the synthesis of [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines by starting from easily available *o*-functionalized aryl azides (Scheme 1). The key step is the formation of the triazole moiety present in intermediates **3** (Scheme 1) by the regioselective thermal cycloaddition of (3-chloroacetonylidene)triphenylphosphorane (**2**) to aryl azides **1a–d** (Harvey approach).[6c,9] This reaction can be visualized as a 1,3-dipolar cycloaddition of the azido group to the C=C bond of the betainic form of the ketophosphorane with subsequent spontaneous elimination of phosphine oxide.

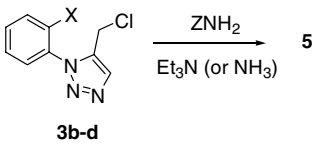
2-Azidobenzyl chloride (**1b**)[10] and 2-azidobenzaldehyde (**1c**)[11] could be obtained in good yields from 2-azidobenzyl alcohol (**1a**)[12] by treatment with thionyl chloride or



Scheme 1. Reaction of the *o*–functionalized aryl azides**1a–d** with (3-chloroacetonylidene)triphenylphosphorane (**2**) to give triazoles **3a–d** and 4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1]benzoxazepine **4**.

PCC, respectively (Scheme 1). The reaction of **1a–c** with **2** led to triazoles **3a–c** in good yields (60–90%)[13] although experimental conditions, that is, temperature and solvent, were crucial for the formation of **3** (see Scheme 1). Thus, an increase of temperature, from 80 °C to reflux, in the reaction of **1a** with **2** led to 4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1]benzoxazepine (**4**) (80%) instead of to **3a**. On the other hand, the reaction of azide **1c** with **2** in toluene at 90 °C led to a mixture of compounds resulting from the Wittig reaction of the phosphorane with the formyl group of **1c** before or after the formation of the triazole ring (not shown in Scheme 1). Triazole **3c** could be alternatively obtained from **3a** by treatment with PCC (60%). Finally, the reaction of methyl 2-azidobenzoate[14] (**1d**) with **2** in refluxing toluene led to triazole **3d** in 90% yield.

The triazole intermediates **3** can act as bis-electrophilic species reacting with different amines to form the benzodiazepine nucleus (Scheme 2 and Table 1). Triazole **3b** was reacted with ammonia, benzylamine or *p*-toluidine to give the corresponding 4*H*,6*H*-[1,2,3]triazolo[1,5-*a*]-[1,4]benzodiazepines **5a–c** in excellent yields (Scheme 2 and Table 1, entries 1–3). In the two latter cases, the presence of triethylamine was necessary.[15] The hetero-



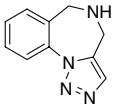
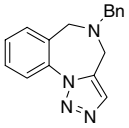
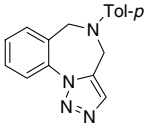
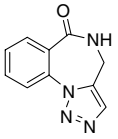
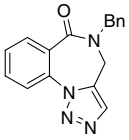
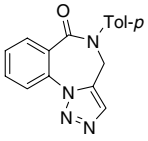
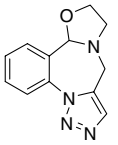
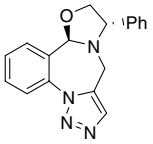
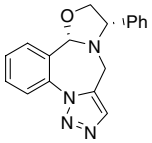
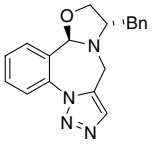
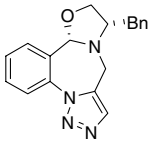
Scheme 2. Triazoles **3b–d** were reacted with different amines to give [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines **5** (see also Table 1 and Scheme 3).

polycyclic structures **5a–c** could be prepared also from triazole **3c** through an alternative route depicted in Scheme 3. Thus, the reaction of **3c** with ammonia in acetonitrile led to 4*H*-[1,2,3]triazolo[1,5-*a*][1,4]benzodiazepine (**6a**) in 87% yield. The subsequent treatment of **6a** with $NaBH_4$ gave **5a** (86%). On the other hand, **3c** was allowed to react with benzylamine or *p*-toluidine and subsequently with $NaBH_4$ to give **5b–c** (50–53%).

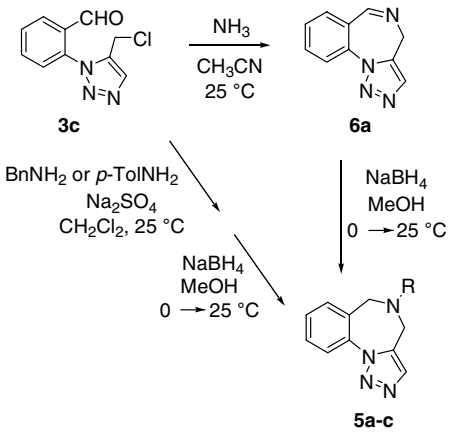
4*H*-[1,2,3]Triazolo[1,5-*a*][1,4]benzodiazepin-6-ones **5d–f** (Table 1, entries 4–6) were prepared by the reaction of triazole **3d** with ammonia, benzylamine or *p*-toluidine respectively in yields ranging 52–87%. Finally, ethanolamine and two other optically active amino alcohols were used as bis-nucleophiles. While the reaction of **3c** and ethanolamine led to the chiral tetracyclic structure **5g** (Table 1, entry 7), the reaction of **3c** with (*S*)-phenylglycinol and (*S*)-phenylalaninol gave *u*-**5h** and *u*-**5i** in excellent yields and high levels of diastereoselection (entries 8–9).[16,17]

In summary, our methodology provides a new and clean synthetic access to [1,2,3]triazolo[1,5-*a*][1,4]benzodiazepines and other derivatives of pharmacological interest using readily available and inexpensive starting materials derived from anthranilic acid. These complex structures can be rapidly assembled using a short sequence of transformations. This new strategy, based on the Harvey approach to the synthesis of triazoles, presents unique properties such as regioselectivity, modularity, mild reaction conditions, and high yields. The rich array of functionalities displayed by the intermediate products **3** provides opportunities for its application in the preparation of combinatorial libraries.

Table 1. [1,2,3]Triazolo[1,5-*a*][1,4]benzodiazepines **5a–i** produced via the reaction depicted in Scheme 2

Entry	Starting material	X	Z	Reaction conditions	Product	Yield[a] (%)
1	**3b**	CH_2Cl	H	Acetonitrile,[b] 25 °C, 16 h	 **5a**	85
2	**3b**	CH_2Cl	Bn	Et_3N, CH_2Cl_2, 25 °C, 48 h	 **5b**	90
3	**3b**	CH_2Cl	*p*–Tol	Et_3N, CH_2Cl_2, reflux, 36 h	 **5c**	72
4	**3d**	COOMe	H	Acetonitrile,[b] 80 °C, 12 h	 **5d**	87
5	**3d**	COOMe	Bn	Et_3N, toluene, reflux, 5 days	 **5e**	80
6	**3d**	COOMe	*p*-Tol	Et_3N, toluene, 140 °C, 14 days	 **5f**	52
7	**3c**	CHO	$HOCH_2CH_2$	Et_3N, CH_2Cl_2, 25 °C, 8 h	 **5g**	93
8	**3c**	CHO		Et_3N, CH_2Cl_2, 25 °C, 72 h	 ***u*-5h**  ***l*-5h**	83 (dr 10:1)[c]
9	**3c**	CHO		Et_3N, CH_2Cl_2, 25 °C, 48 h	 ***u*-5i**  ***l*-5i**	80 (dr 10:1)[c]

[a] After purification by chromatography.
[b] In this case the addition of Et_3N was not necessary.
[c] Determined by ^1H NMR analysis of characteristic signals directly on the crude product (error ±5% of the stated value).



Scheme 3. Alternative route to that shown in Table 1 (entries 1–3) for the synthesis of **5a–c** by starting from triazole **3c**.

Acknowledgements

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12. Smolinsky, G. *J. Org. Chem.* **1961**, *26*, 4108–4110.
13. *Experimental procedure for the synthesis of* **3b**: A solution of **1b** (1.42 g; 8.50 mmol) and phosphorane **2** (2.00 g; 5.67 mmol) in toluene (50 mL) was stirred under reflux for 6 h. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography eluting with 1:2 AcOEt/hexane ($R_f = 0.23$); yield 90%; mp 68–69 °C (colorless prisms, Et_2O); IR (Nujol) 1503, 1282, 1268, 1232, 1113, 1103, 980, 840, 776, 725, 671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.37 (s, 2H), 4.51 (s, 2H), 7.45 (d, 1H, $J = 7.7$ Hz), 7.56 (td, 1H, $J = 7.6$ Hz, $J = 1.7$ Hz), 7.60–7.68 (m, 2H), 7.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.0 (t), 41.3 (t), 127.8 (d), 129.7 (d), 131.2 (d), 131.4 (d), 133.7 (s), 133.8 (d), 135.2 (s), 135.5 (s); MS (EI, 70 eV) *m/z* (rel int) 245 (M^++4, 13), 243 (M^++2, 21), 241 (M^+, 29), 230 (32), 180 (34), 178 (100), 143 (63), 142 (60), 125 (59), 116 (28), 115 (34), 89 (56), 63 (25). Anal. Calcd for $C_{10}H_9Cl_2N_3$ (242.11): C, 49.61; H, 3.75; N, 17.36. Found: C, 49.84; H, 3.93; N, 17.36.
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15. *Experimental procedure for the synthesis of* **5a**: A slow stream of ammonia gas was continually bubbled through a solution of **3b** (0.20 g; 0.83 mmol) in acetonitrile (10 mL) at 25 °C for 10 min. The reaction mixture was kept in a sealed tube and stirred at the same temperature for 16 h. After removal of the solvent under reduced pressure, the residue was treated with 5%, aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by chromatography with Et_3N-deactivated silica gel eluting with 5:1 AcOEt/MeOH ($R_f = 0.30$); yield 85%; mp 124–125 °C (colorless prisms, Et_2O); IR (nujol) 3312, 1492, 1228, 1132, 977, 835, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.61 (broad s, 1 H, NH), 3.81 (s, 2H), 4.02 (s, 2H), 7.41–7.47 (m, 2H), 7.53 (ddd, 1H, $J = 7.8$ Hz, $J = 7.1$ Hz, $J = 2.0$ Hz), 7.70 (s, 1H), 7.92 (dd, 1H, $J = 7.8$ Hz, $J = 1.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 38.8 (t), 48.6 (t), 122.7 (d), 129.1 (d), 129.2 (d), 130.0 (d), 131.2 (s), 132.0 (d), 135.3 (s), 136.6 (s); MS (EI, 70 eV) *m/z* (rel int) 186 (M^+, 12), 157 (100), 130 (22), 103 (22), 102 (25). Anal. Calcd for $C_{10}H_{10}N_4$ (186.21): C, 64.50; H, 5.41; N, 30.09. Found: C, 64.26; H, 5.80; N, 30.04.
16. The sense and level of stereocontrol observed in the formation of **5h**,**i** follow similar trends to those previously reported for the reactions of the chiral amino alcohols

with other aldehydes (a) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Qais, N. *Tetrahedron Lett.* **1988**, *29*, 6949–6950; (b) Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. *Tetrahedron* **1990**, *46*, 5909–5920; (c) Hatano, K.; Kurono, Y.; Kuwayama, T.; Tamaki, H.; Yashiro, T.; Ikeda, K. *J. Chem. Soc., Perkin Trans. 2* **1992**, 621–628; (d) Penhoat, M.; Leleu, S.; Dupas, G.; Papamicaël, C.; Marsais, F.; Levacher, V. *Tetrahedron Lett.* **2005**, *46*, 8385–8389.

17. Experimental procedure for the synthesis of *u*-**5h** and *l*-**5h**: (*S*)–phenylglycinol (0.09 g; 0.68 mmol) was added to a solution of **3c** (0.15 g; 0.68 mmol) and Et_3N (0.21 g, 2.03 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at 25 °C for 72 h, then washed with 5%, aqueous $NaHCO_3$ (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by chromatography with silica gel eluting with 1:1 AcOEt/hexane ($R_f = 0.44$) to give a mixture of *u*-**5h** and *l*-**5h** in a 10:1 ratio (83% overall yield); colorless oil; IR (neat) 1608, 1588, 1487, 1454, 1372, 1340, 1280, 1232, 1189, 1133, 1088, 1038, 980, 911, 840, 762, 734, 702, 647 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.27 (d, 1H, $J = 13.5$ Hz, H_u), 3.81–3.87 (m, 2H, $H_u + H_l$), 3.97–4.03 (m, 3H, $2H_u + H_l$), 4.16 (dd, 1H, $J = 15.8$ Hz, $J = 0.7$ Hz, H_l), 4.22 (dd, 1H, $J = 9.2$ Hz, $J = 6.6$ Hz, H_l), 4.34 (dd, 1 H, $J = 7.6$ Hz, $J = 6.6$ Hz, H_l), 4.45 (dd, 1H, $J = 7.8$ Hz, $J = 6.9$ Hz, H_u), 5.45 (s, 1H, H_l), 5.66 (s, 1H, H_u), 7.32–7.62 (m, 15H, $7H_u + 8H_l$), 7.77 (s, 1H, H_u), 7.74–7.70 (m, 2H, $H_u + H_l$), 7.88 (dd, 1H, $J = 7.8$ Hz, $J = 1.4$ Hz, H_u), 8.22 (dd, 1H, $J = 8.1$ Hz, $J = 1.2$ Hz, H_l); ^{13}C NMR ($CDCl_3$) δ 41.1 (t, C_u), 43.5 (t, C_l), 65.9 (d, C_u), 69.1 (d, C_l), 72.9 (t, C_l), 74.7 (t, C_u), 92.1 (d, C_u), 92.7 (d, C_l), 122.8 (d, C_l), 123.3 (d, C_u), 125.3 (d, C_l), 127.4 ($2 \times$ d, C_u), 127.8 ($2 \times$ d, C_l), 128.28 (d, C_u), 128.30 (d, C_l), 128.5 (d, C_l), 128.7 (d, C_u), 128.8 ($2 \times$ d, C_l), 128.9 ($2 \times$ d, C_u), 129.0 (d, C_u), 129.3 (d, C_l), 129.9 (s, C_u), 130.2 (d, C_u), 131.5 (s, C_l), 131.8 (d, C_l), 132.2 (d, C_u), 133.7 (s, C_u), 134.1 (s, C_u), 134.2 (s, C_l), 134.4 (s, C_l), 136.0 (s, C_l), 137.3 (s, C_u); MS (EI, 70 eV) *m*/*z* (rel int) 304 (M^+, 33), 303 (100), 275 (90), 245 (40), 155 (32), 104 (40), 103 (32), 91 (55), 77 (33). HRMS-EI *m*/*z*: [M^+–H] Calcd for $C_{18}H_{15}N_4O$, 303.124586; found, 303.123934.