Extending Triazolyl-Based Release under Mildly Acidic Conditions To Give Aniline Derivatives

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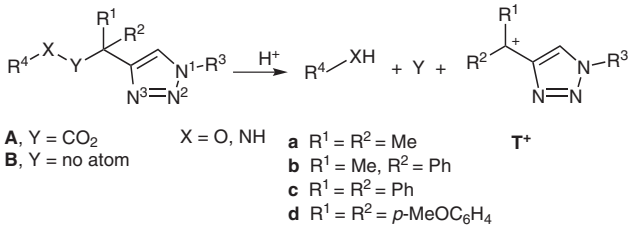
Received 8 December 2011; revised 19 January 2012

Abstract: Triazolyl derivatives of anilines were prepared and evaluated as releasing systems at mildly acidic pH values. Two triazolyl derivatives showed convenient pH sensitivity, being stable at pH 7.3 and rapidly hydrolyzed at pH values below 5. A generalized mechanism is proposed from additional theoretical investigations.

Key words: hydrolysis, alkynes, azides, cycloaddition, amines, protonation

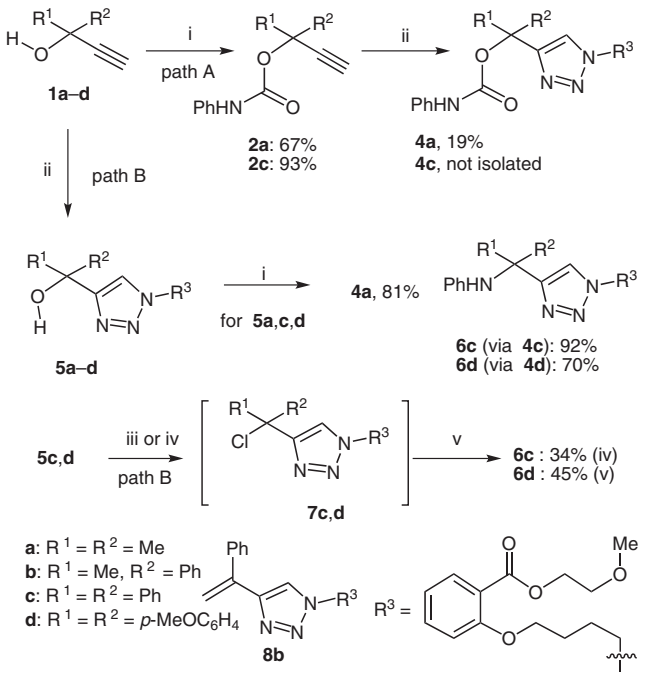
Drug delivery systems (DDS) are developed to exploit endocytosis[1] and enhance permeability and retention effects,[2] with progressive or differentiated release being extensively investigated.[3] Covalent acid-sensitive linkers are used to connect drugs to vectors[4] to exploit the acidic process of endocytosis. We recently described amine[5] and alcohol[6] release (Scheme 1, X = NH or O respectively) based on an acid-sensitive triazolyl system obtained by click chemistry[7] and report herein new findings for the release of aniline.



Scheme 1 Principle of triazolyl-based acid-sensitive systems

Two synthetic pathways were investigated to prepare aniline carbamates **A** (Scheme 1, Y = CO_2, R^4 = Ph) and alkylanilines **B** (Scheme 1, Y = no atom, R^4 = Ph). In path A (Scheme 2), propargylic carbamates **2** were prepared from alcohols **1**. The reaction with alcohols **1a** and **1c** proceeded in good yields, however, although alcohols **1b** and **1d** were consumed, the corresponding carbamates **2b** and **2d** were probably unstable and could not be isolated.[8] Cycloaddition of **2a** with azide **3** gave carbamate **4a** in modest yield. The cycloaddition of **2c** resulted in decomposition. In path B, the known alcohols **5a–d** were prepared in high yields and reacted with phenyl isocyanate to give carbamates **4**. Carbamate **4a** was isolated in higher yield than that obtained using path A. The syntheses of carbamates **4b–d** remained problematic. Alcohol **5b** gave carbamate **4b** together with the inseparable alkene **8b**. For alcohols **5c** and **5d**, two rearranged amine derivatives **6c** and **6d** were isolated in very high yields instead of the expected carbamates **4c** and **4d**. The structures of alkylamines **6c** and **6d** were confirmed by their preparation from alcohols **5** (path B), via chlorides **7** and substitution with aniline (Scheme 2, iii–v). Since dianisyl chlorides can easily be converted into alcohols,[9] this may explain the low yields observed with the chlorination method. Amines **6c** and **6d** were obtained in moderate yields compared to the in situ rearrangement of carbamates **4c** and **4d**. Derivatives **6a** and **6b** were not prepared because they were expected to be stable at low pH. The syntheses of amines **6c** and **6d** appeared to be more effective via the rearrangement of carbamates **4c** and **4d**, which are probably formed in situ.

The carbamate **4a** and alkylamines **6c** and **6d** were submitted to acidic hydrolysis (citrate buffer for pH 4.3 and TRIZMA buffer for physiological pH). Half-lives ($t_{1/2}$) are



Scheme 2 *Reagents and conditions*: (i) PhNCO, heptane, Et_3N cat., reflux, 30 min; (ii) azide **3** (R^3N_3), CuI, THF–H_2O (1:1), 24 h, 20 °C; (iii) HCl, CH_2Cl_2, reflux; (iv) $SOCl_2$, CH_2Cl_2, reflux; (v) aniline, overnight.

SYNTHESIS 2012, 44, 1090–1094
Advanced online publication: 24.02.2012
DOI: 10.1055/s-0031-1289719; Art ID: T113611SS

reported for carbamate **4a** and amines **6c** and **6d** (Table 1). The carbamate **4a** was stable at all pH values. The amine derivatives **6c** and **6d** were rapidly hydrolyzed at pH 4.3 and stable at pH 7.3, which indicates that these compounds are very good candidates for further development; acidic maturation during endocytosis being around one hour. These findings prompted us to make additional theoretical calculations for these new derivatives.[5]

Table 1 Half-Life Values ($t_{1/2}$) for Carbamate **4a** and Amines **6c** and **6d**

Aniline	Y	R^1	R^2	$t_{1/2}$ (min)	
				pH 4.3	pH 7.3
4a	CO_2	Me	Me	43200	stable
6c	–	Ph	Ph	77.3	stable
6d	–	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	0.35	stable

Calculations indicated that the preferred protonation sites were the N-3 nitrogen atom for carbamates **4** and the amine nitrogen atom for amines **6** (Figure 1). Compared to previous results obtained with benzylamine,[5] the preferences for site-specific protonation of carbamates **4** and amines **6** were less pronounced; aniline being less nucleophilic. Initial N-3 protonation of **4** activates the hydrolysis by a proton transfer to the carbonyl group. This participation appeared critical and general (Scheme 3). To account for the medium sensitivity of carbamate **4** and alkylamine **6**, the free energies (ΔG^A_{water} for **4** and ΔG^B_{water} for **6**) were computed according to Equation 1.

After the initial protonation, the decomposition of **A-N^{3}H$^+$** and **B-NH$^+$** species to the carbocation **T$^+$** (Scheme 3, X = NH) is correlated with the electron-donating effect of the R^1 and R^2 groups (Table 2).

We then applied these results to substituted aniline. Because our group has been working on the design of HDAC inhibitors,[10] we focused on 2-substituted aniline, which is a key functional group in this class of inhibitors. A general

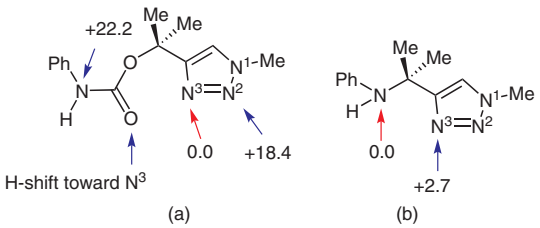
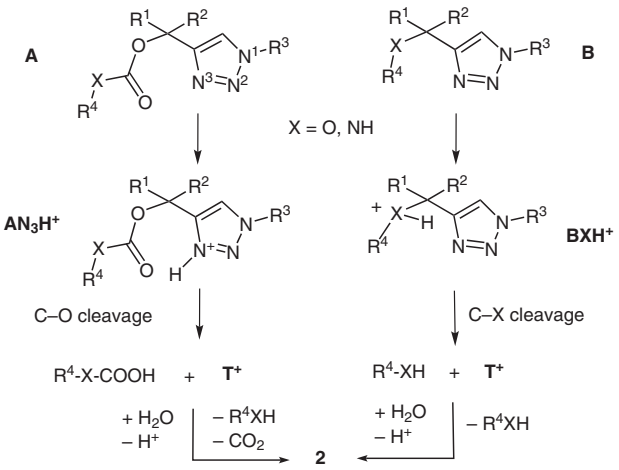


Figure 1 Relative free energies of protonation sites (kcal/mol) at the B3LYP/6-31G(d,p) level for (a) aniline carbamate **4** and (b) alkylkaniline **6** models (R^1 = R^2 = Me; R^3 = Me)

A-N^{3}H$^+$ → Ph-NH-CO_2H + **T$^+$** ΔG^A_{water}
B-NH$^+$ → Ph-NH_2 + **T$^+$** ΔG^B_{water}
with:
$\Delta G^A_{water} = G(\mathbf{T^+})_{water} + G(\text{Ph-NH-CO}_2\text{H})_{water} - G(\mathbf{A\text{-}N^3H^+})_{water}$
$\Delta G^B_{water} = G(\mathbf{T^+})_{water} + G(\text{Ph-NH}_2)_{water} - G(\mathbf{B\text{-}NH^+})_{water}$

Equation 1



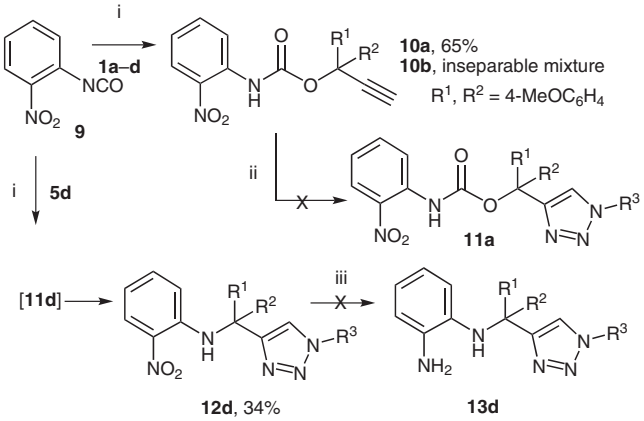
Scheme 3 Proposed generalized hydrolysis mechanism for triazolyl derivatives **A** and **B**

approach was planned with 2-substituted aniline linked to the releasing system **5** to provide advanced intermediates **11** or **13** (Scheme 4). We selected the isocyanate **9** as starting material because the nitro group is reducible and because direct use of 2-aminoaniline was not suitable for isocyanate preparation. Isocyanate **9** was reacted with alcohols **1a–d** as depicted in path A (Scheme 4), to give carbamate **10a** in good yield; carbamate **10b** was obtained as a mixture, whereas **10c** and **10d** were not obtained. Carbamate **10a** was found to be unstable during the click reaction, regardless of the conditions used. Path B was then investigated using the alcohol **5d** only, because of its expected rapid release as demonstrated for aniline. Isocyanate **9** was reacted with alcohol **5d** and carbamate **11d** (which was not observed directly) was again converted into nitroaniline **12d** in situ. The lower yield of the latter compared to that obtained with the unsubstituted aniline was due to difficulties during purification, and compound **12d** was finally isolated along with trace amounts of the starting alcohol **5d**. Its reduction to the corresponding amino derivative **13d** led to only decomposed products under $SnCl_2$ conditions.

The hydrolysis was measured for **12d** only in pH 4.3 buffer containing acetonitrile, and the $t_{1/2}$ (after subtraction of the initial residual alcohol **5d**) was estimated to be 150 min (Figure 2, left). This slower release, compared

Table 2 Computed Aqueous Solution Free Energies (ΔG_{water} in kcal/mol) for Protonated Triazolylaniline Carbamates **A-N^{3}H$^+$** and Triazolylalkylanilines **B-NH$^+$** Decomposition Reactions

Series	R^1	R^2	**4**, **A-N^{3}H$^+$** ΔG^A_{water}	**6**, **B-NH$^+$** ΔG^B_{water}
a	Me	Me	+1.0	+4.0
b	Me	Ph	–4.0	–1.9
c	Ph	Ph	–10.2	–10.9
e	*p*-MeC_6H_4	*p*-MeC_6H_4	–14.3	–14.0
d	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	–17.6	–17.7



Scheme 4 *Reagents and conditions*: (i) heptane, Et_3N cat., reflux, 30 min; (ii) azide **3** (R^3N_3), CuI, solvents, 20 °C; (iii) $SnCl_2$, EtOH.

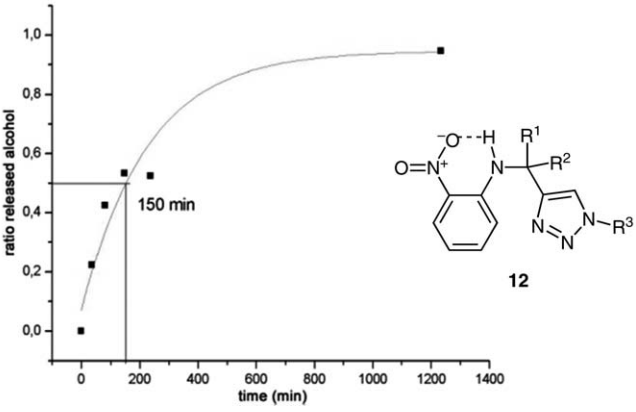


Figure 2 Hydrogen bond in compound **12d** and hydrolysis determination at pH 4.3

with aniline derivatives **6d**, can be explained by the effect of the nitro group, where the electron-withdrawing effect and an intramolecular hydrogen bond[11] (Figure 2, right) participate in reducing the nucleophilic character of the amine, decreasing the protonation efficiency and, in turn, increasing the acidity of the hydrogen atom. This increase in acidity was confirmed by the ^{1}H NMR signal of this hydrogen atom, which was observed at δ = 9.6 ppm, instead of being close to δ = 6 ppm observed for the NH signals in compounds **6**. These results indicate that, in the case of aniline, the reaction has an additional parameter resulting from mesomeric effects originating from the aniline substituents, and probably also its position on the aniline ring.

In summary, an efficient, tunable release of aniline from a triazolyl-based acid-sensitive system has been developed. This work confirmed the rearrangement of aromatic carbamates **4** (or **11**) into the corresponding amines **6** (or **12**) in high yields, and has shown the approach to be a practical strategy for unsubstituted aniline. Direct linking of substituted anilines to our system (path B) should be a more general route when the isocyanate strategy is not applicable, despite the moderate yields obtained. Recycling of the unreacted material should be possible. Biological applications with relevant bioactive substituted anilines as well as other functional groups are being developed. Theoretical calculations allowed generalization of the proposed hydrolysis mechanism, the triazole ring being critical for carbamates. Complementary mechanistic investigations are warranted, which should clarify the degree of water assistance and establish more precise energy barriers and substituent effects for anilines.

After work up, the organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum unless otherwise noted. Purifications were achieved by flash chromatography, with EtOAc and PE on silica gel. Petroleum ether (PE), where used, had boiling range 35–60 °C. Melting points were determined with a Kofler apparatus. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance DPX at 400 and 100 MHz, respectively. NMR spectra were recorded in $CDCl_3$ or acetone-d_6 and chemical shifts are given in ppm relative to TMS. High-resolution mass spectra were obtained at CRMPO, Rennes, France.

1,1-Dimethylprop-2-ynyl Phenylcarbamate (2a)

To a solution of **1a** (580 μL, 5.61 mmol) in heptane (30 mL) was added Et_3N (390 μL, 2.81 mmol). The solution was heated at reflux and phenyl isocyanate (300 μL, 2.81 mmol) was added. After heating to reflux for 2 h, the solution was cooled to r.t., dissolved in Et_2O (25 mL) and washed with $KHSO_4$ (1 M, 3 × 20 mL), and brine (2 × 25 mL), dried, filtered, concentrated and purified by flash chromatography (PE–EtOAc, 9:1) to afford **2a**.

Yield: 390 mg (67%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.9 Hz, 2 H), 7.26 (m, 2 H), 7.03 (m, 1 H), 6.54 (s, 1 H), 2.56 (s, 1 H), 1.73 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 137.8, 129.0, 123.4, 118.6, 84.9, 72.4, 72.2, 29.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{13}NO_2Na$: 226.08440; found: 226.0846.

1,1-Diphenyl-prop-2-ynyl Phenylcarbamate (2c)

To a solution of **1c** (0.60 g, 2.88 mmol) in heptane (20 mL) was added Et_3N (200 μL, 1.44 mmol). The solution was heated at reflux and phenyl isocyanate (160 μL, 1.44 mmol) was added. The solution was heated at reflux for 2 h more until a white precipitate appeared. The solution was extracted with Et_2O (10 mL) and washed with $KHSO_4$ (1 M, 3 × 10 mL), then brine (2 × 10 mL). The organic layer was dried, filtered, concentrated, and purified by flash chromatography (PE–EtOAc, 100:0–60:40) to afford **2c**.

Yield: 440 mg (93%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (m, 4 H), 7.36 (m, 7 H), 7.28 (m, 3 H), 7.04 (t, *J* = 7.4 Hz, 1 H), 6.84 (s, 1 H), 3.05 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 141.9, 137.5, 128.9, 128.5, 128.3, 128.1, 126.1, 123.5, 82.5, 79.6, 78.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{17}NO_2Na$: 350.1157; found: 350.1160.

2-Methoxyethyl 2-{4-[4-(1-Methyl-1-phenylcarbamoyloxyethyl)[1,2,3]triazol-1-yl]butoxy}benzoate (4a)

Prepared as described for **2c** from **5a** (0.2 g, 0.53 mmol), heptane (20 mL), THF (5 mL), Et_3N (15 μL, 0.11 mmol), and PhNCO (75 μL, 0.69 mmol). Purified by flash chromatography (PE–EtOAc, 90:10–0:100).

Yield: 214 mg (81%); colorless oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 8.57 (s, 1 H), 7.99 (s, 1 H), 7.72 (dd, *J* = 1.7, 7.7 Hz, 1 H), 7.49 (m, 3 H), 7.24 (m, 2 H), 7.08 (dd, *J* = 0.9, 8.5 Hz, 1 H), 6.98 (m, 2 H), 4.51 (t, *J* = 7.1 Hz, 2 H),

4.38 (m, 2 H), 4.08 (t, *J* = 6.0 Hz, 2 H), 3.65 (m, 2 H), 3.32 (s, 3 H), 2.17 (m, 2 H), 1.85 (s, 3 H), 1.80 (m, 2 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 166.9, 159.1, 153.2, 152.3, 140.4, 134.2, 132.0, 129.5, 123.2, 122.4, 121.8, 120.9, 119.1, 114.2, 77.4, 71.2, 68.7, 64.4, 58.8, 50.3, 28.1, 27.9, 26.9.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{26}H_{32}N_4O_6Na$: 519.22195; found: 519.2210.

2-Methoxyethyl 2-{4-[4-(Diphenylphenylaminomethyl)[1,2,3]triazol-1-yl]butoxy}benzoate (6c);
Method A (via Carbamate)

To a solution of heptane (40 mL) and anhydrous THF (5 mL) under a nitrogen atmosphere were added **5c** (0.3 g, 0.6 mmol) and Et_3N (17 μL, 0.12 mmol). The solution was heated at reflux and PhNCO (130 μL, 1.2 mmol) was added. After heating a reflux for 2 h, a white precipitate could be observed. The solution was cooled, diluted with EtOAc (25 mL) and washed with brine (2 × 20 mL). The organic layer was dried, filtered, concentrated and purified by flash chromatography (PE–EtOAc) to afford the triazolyl amine **6c** as a yellow oil.

Method B (via Chloride)

To a mixture of **5c** (0.2 g, 0.4 mmol) in anhydrous CH_2Cl_2 (10 mL) under a nitrogen atmosphere was added HCl (2 M in Et_2O, 299 μL, 0.6 mmol). The solution was heated at reflux for 1 h, then Et_3N (139 μL, 1.0 mmol) and aniline (55 μL, 0.60 mmol) were added. The mixture was heated at reflux for 2 h and then cooled. The solvent was removed and the residue was purified by flash chromatography (PE–EtOAc + 1% Et_3N) to afford **6c** as a colorless oil.

Yield (method A): 319 mg (92%).

Yield (method B): 79 mg (34%).

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.79 (s, 1 H), 7.71 (dd, *J* = 1.8, 7.7 Hz, 1 H), 7.55 (m, 4 H), 7.48 (m, 1 H), 7.27 (m, 4 H), 7.20 (m, 2 H), 7.07 (d, *J* = 8.3 Hz, 1 H), 6.99 (dt, *J* = 0.8, 7.6 Hz, 1 H), 6.87 (m, 2 H), 6.48 (m, 3 H), 6.01 (s, 1 H), 4.49 (t, *J* = 6.9 Hz, 2 H), 4.31 (m, 2 H), 4.02 (t, *J* = 6.0 Hz, 2 H), 3.62 (m, 2 H), 3.30 (s, 3 H), 2.10 (m, 2 H), 1.65 (m, 2 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 166.8, 159.1, 152.5, 147.3, 146.3, 134.2, 132.0, 129.2, 128.8, 128.7, 127.6, 125.6, 121.7, 120.9, 117.9, 117.2, 114.2, 71.1, 68.7, 66.3, 64.4, 58.8, 50.2, 27.9, 26.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{35}H_{36}N_4O_4Na$: 599.26288; found: 599.2629.

2-Methoxyethyl 2-(4-{4-[Bis(4-methoxyphenyl)phenylaminomethyl][1,2,3]triazol-1-yl}butoxy)benzoate (6d);
Method A (via Carbamate)

Prepared as described for **6c** from **5d** (0.216 g, 0.38 mmol), heptane (30 mL), anhydrous THF (5 mL), Et_3N (11 μL, 0.077 mmol) and PhNCO (63 μL, 0.58 mmol).

Method B (via Chloride)

Prepared as described for **6c** from **5d** (0.2 g, 0.36 mmol), CH_2Cl_2 (15 mL), $SOCl_2$ (30 μL, 0.42 mmol) and Et_3N (150 μL, 1.07 mmol). Purified by flash chromatography (two times; PE–EtOAc, 80:20 → 30:70 and 2% Et_3N) to afford **6d** with traces of starting **5d**.

Yield (method A): 170 mg (70%).

Yield (method B): 114 mg (50%).

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.73 (m, 2 H), 7.47 (ddd, *J* = 1.8, 7.4, 8.5 Hz, 1 H), 7.43 (m, 4 H), 7.05 (dd, *J* = 0.6, 8.5 Hz, 1 H), 6.99 (dt, *J* = 1.0, 7.6 Hz, 1 H), 6.88 (dd, *J* = 7.3, 8.7 Hz, 2 H), 6.81 (m, 4 H), 6.49 (m, 3 H), 5.91 (s, 1 H), 4.47 (t, *J* = 7.0 Hz, 2 H), 4.32 (m, 2 H), 4.01 (t, *J* = 6.0 Hz, 2 H), 3.74 (s, 6 H), 3.62 (m, 2 H), 3.30 (s, 3 H), 2.10 (m, 2 H), 1.66 (m, 2 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 166.8, 159.4, 159.2, 153.3, 147.4, 138.5, 134.2, 132.0, 130.4, 128.8, 125.2, 121.7, 120.9, 117.7, 117.1, 114.2, 113.9, 71.2, 68.7, 65.3, 64.4, 58.9, 55.5, 50.2, 27.9, 26.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{37}H_{40}N_4O_6Na$: 659.28401; found: 659.2838.

1,1-Dimethyl-prop-2-ynyl 2-Nitrophenylcarbamate (10a)

Prepared as described for **2a** from **1a** (1.16 mL, 11.12 mmol), heptane (100 mL), Et_3N (313 μL, 2.24 mmol) and 2-nitrophenylisocyanate (1.00 g, 6.09 mmol). Purification by flash chromatography (PE–EtOAc, 9:1) afforded carbamate **10a**.

Yield: 983 mg (65%); yellow solid; mp 108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 8.61 (d, *J* = 8.6 Hz, 1 H), 8.20 (d, *J* = 8.5 Hz, 1 H), 7.62 (dd, *J* = 7.6, 8.5 Hz, 1 H), 7.13 (dd, *J* = 7.5, 8.2 Hz, 1 H), 2.62 (s, 1 H), 1.78 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3, 136.1, 135.9, 135.4, 125.9, 122.3, 120.8, 84.4, 73.2, 72.9, 29.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}N_2O_4Na$: 271.06948; found: 271.0696.

2-Methoxyethyl 2-(4-{4-[Bis(4-methoxyphenyl)-2-nitrophenylaminomethyl]-[1,2,3]triazol-1-yl}butoxy)benzoate (12d)

Prepared as described for **6d** from **5d** (280 mg, 0.5 mmol), heptane (35 mL), anhydrous THF (7 mL), Et_3N (14 μL, 100 μmol), and 2-nitrophenylisocyanate (123 mg, 0.75 mmol). Purification by flash chromatography (PE–EtOAc, 80:20→30:70 and 2% Et_3N) afforded **12d** with traces of starting **5d**.

Yield: 124 mg (34%).

^{1}H NMR (400 MHz, acetone-d_6): δ = 9.62 (s, 1 H), 8.13 (dd, *J* = 8.6, 1.52 Hz, 1 H), 7.89 (s, 1 H), 7.75 (m, 2 H), 7.51 (m, 2 H), 7.09 (m, 2 H), 7.01 (td, *J* = 7.5, 1.0 Hz, 2 H), 6.90 (d, 4 H), 6.64 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1 H), 6.5 (dd, *J* = 8.8, 1.1 Hz, 1 H), 4.53 (t, *J* = 7.0 Hz, 2 H), 4.31 (m, 2 H), 4.06 (t, *J* = 6.0 Hz, 2 H), 3.79 (s, 6 H), 3.64 (t, *J* = 8.3 Hz, 2 H), 3.33 (s, 3 H), 2.16 (m, 2 H), 1.73 (m, 2 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 166.5, 159.8, 159.5, 152.2, 145.0, 140.5, 137.0, 135.1, 134.2, 132.0, 130.1, 126.4, 125.1, 120.9, 120.1, 116.8, 114.4, 114.3, 114.2, 74.5, 71.1, 68.8, 64.4, 58.8, 50.4, 27.8, 26.6.

HPLC Monitoring

A solution of **4a/6c/6d** (0.4 mL of a 0.5 mg/mL solution in MeCN) were added to citrate buffer (1.6 mL) under vigorous stirring. Samples were injected at different times and analyzed with an automated Waters LaChrom Elite equipped with a diode-array detector (DAD Hitachi L-2455; 200–400 nm), an autosampler (Hitachi L-2200), a pump (Hitachi L-2130), and a reversed-phase HPLC column (Lichrocart 150–4,6 purospher STAR).

^{1}H NMR Monitoring

Hydrolysis of **12d** was followed by ^{1}H NMR spectroscopic analysis. A reaction mixture (10 mL) was prepared using the same concentration ratios used for HPLC monitoring (buffer, MeCN). Samples (1 mL) were collected at regular times from this reaction mixture, neutralized with 1 M $KHCO_3$, extracted with EtOAc (3 × 5 mL), dried, and concentrated to give a crude material, which was directly analyzed by ^{1}H NMR. Typical ^{1}H NMR signals from the triazole (C-H) and anisyl (Ar-H and OMe) groups were different in compound **12d** and released alcohol **5d** and were used to obtain average values for $t_{1/2}$.

Theoretical Calculations
All structures were studied using the B3LYP method as previously described,[5] with the Gaussian 09 package.

Acknowledgment

The authors thank the Centre National de la Recherche Scientifique (CNRS) and the Agence National de la Recherche (ANR) for financial support and ANR for a grant to R.D.

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