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Click chemistry with ynamides

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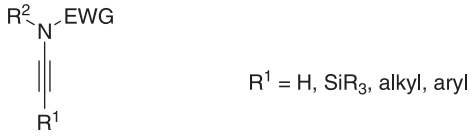
Abstract—A series of diversely 1-substituted 4-amino 1,2,3-triazoles were synthesized by [3+2] cycloaddition between azides and ynamides. This copper catalyzed process represents the first examples of a 'click reaction' employing ynamides and should expand the scope of the ynamide chemistry both synthetically and industrially. Various azides (even highly functionalized) were allowed to react with *N*-benzyl, *N*-tosyl ynamide to give the corresponding triazole adducts in high yield and with very high levels of regioselectivity.

1. Introduction

Over the last decade, the chemistry of electron deficient variants of ynamines (ynamides) has exploded. This is mainly due to the emergence of straightforward synthetic protocols to obtain this particular synthon[1] in which the nitrogen atom is a member of an electron-withdrawing group (Scheme 1) providing superior stability when compared to the parent ynamines.



Scheme 1. Stabilized ynamines.

Having in hand robust protocols to synthesize ynamides, numerous transformations of these compounds have been reported among which the metal catalyzed transformations are the more abundant. We can for instance mention the reactions in which internal ynamides are involved in carbometallation,[2] RCM,[3] Ru-catalyzed cycloadditions[4] or titanation.[5] Focussing on terminal alkynes ($R^1=H$ in Scheme 1), similar reactivity has been evidenced including RCM,[6] [4+2] cycloaddition,[7] cyclotrimerizations,[8] Pauson–Khand reaction[9,10], hydro-[11a] and carboboration,[11b] hydro- or silylstannation,[12a–d] Bu_3SnH-induced radical cyclization,[12e] titanium-mediated couplings,[13] platinum dichloride-catalyzed cycloisomerisation,[14] Negishi-coupling,[15] Glaser-type homocoupling[16] as well as Sonogashira cross-couplings.[17]

2. Results and discussion

Surprisingly, to the best of our knowledge, no [3+2] dipolar cycloaddition of ynamides with azides has been reported. This synthetic route would open access to amino triazole, a scaffold found in bioactive molecules.[18] In addition, the recent discovery of copper catalysis[19] of this 1,3-dipolar cyclization has revitalized interest of the synthetic community in this coupling strategy.[20] Indeed, addition of copper(I) salts allows, besides clean reaction and an increase of the reaction rate, a complete control of the regioselectivity observed in this process (1,4-disubstituted 1,2,3-isomer is obtained as the sole product). Therefore, encouraged by the reported relative stability of terminal ynamides towards copper(I) salts,[17] we decided to explore the feasibility of the 'click chemistry' with compounds of the general formula depicted in Scheme 1 ($R^1=H$).[21] Using two sets of previously described conditions for successful 'click' reactions, preliminary experiments were conducted with *N*-benzyl *N*-tosyl ynamide, an imidazolidinone based ynamide as well as the *N*-ethynyl 1,3-oxazolidinone in the presence of *N*-Boc 2-azido ethylamine (Scheme 2).

Whilst the reactions with the two heterocyclic based ynamides **1** and **3** resulted in extensive degradation of the starting material, the same conditions applied to *N*-tosyl *N*-benzyl ynamide **2** cleanly afforded the expected cyclized product with only minor by-products. Therefore, we decided to select ynamide **2** as one of the coupling partner in 'click

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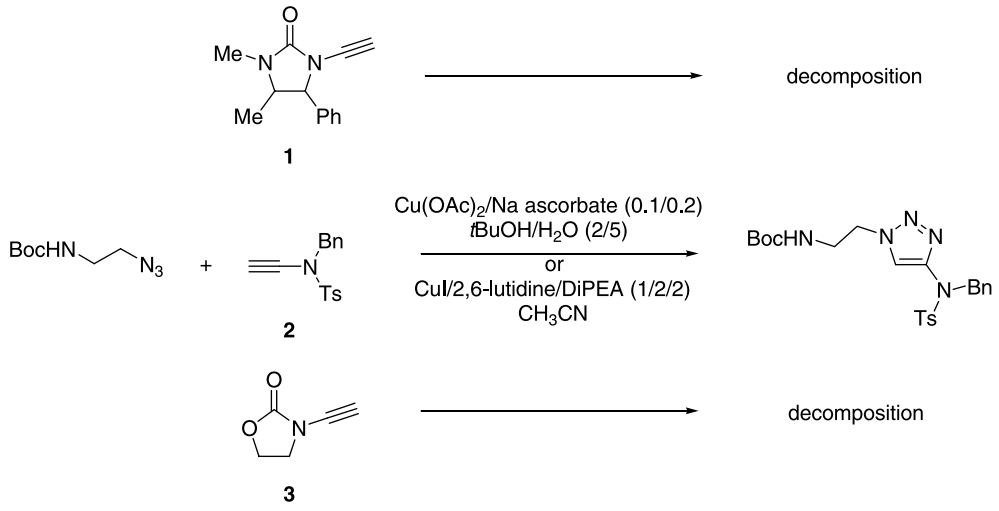


Scheme 2. Preliminary attempts of 'click chemistry' with ynamides.

chemistry'. A wide range of azides were tested for [3+2] cyclization with **2** and the results are summarized in Table 1.

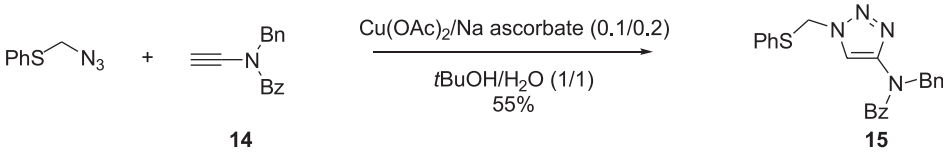
As already mentioned in numerous reports, the click conditions can be applied to structures that bear a wide variety of functional groups. For instance, in our case the first example was conducted with an azide bearing a carbamate (entry 1). It is, however, noteworthy that the amino group of an amine does not need to be protected to give successful cyclization (entry 2). Obviously very simple azides (benzylic or aliphatic) can be reacted with ynamide **2** affording benzyl- or homobenzyl-substituted triazoles (entries 3 and 4) despite a lower yield for compound **6**. One should keep in mind that deprotection of the 1-benzyl group of compound **6** by hydrogenolysis should afford a free amino group that could serve as a starting point for further introduction of functional diversity on triazoles. A slightly different aromatic azide bearing a thio ether group has also proven to be a good candidate for such reaction (entry 5). In an effort to improve the complexity of starting azides, a phenol derivative bearing amide functionality was also cyclized with **2** (entry 6). In order to target our approach to potentially bioactive compounds, ynamide **2** was reacted with carbohydrates based azides with excellent yields (entries 7 and 8). Even an amino-acid based azide has been clicked with **2** to yield a new heteroaromatic alanine derivative (entry 9). Finally, AZT could also be coupled with **2** to furnish compound **13** with a moderate yield (entry 10). It is quite clear from the above results that ynamides can react with various azides in [3+2] cycloaddition. Even highly functionalized azides (entries 6–10) are good partners for ynamides in copper catalyzed 1,3-dipolar cycloadditions.

As mentioned above, in order to diversify the functional groups on the triazole scaffold it is mandatory to have easily removable protective groups. This is something that can be hardly achieved with *N*-tosyl group present in ynamide **2**. Therefore, we also tried to involve ynamide **14** in the 1,3-dipolar cycloaddition (Scheme 3).

Despite the unsuccessful cyclization previously encountered with ynamides **1** and **3** (Scheme 2), erroneously first assigned to a lack of reactivity of carbamates or urea derived ynamides, we were pleased to observe a clean conversion of compound **14** as checked by ^{1}H NMR of the crude reaction mixture. Purification afforded compound **15** with a satisfactory yield (55%).

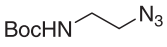
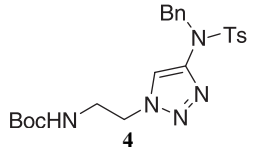
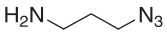
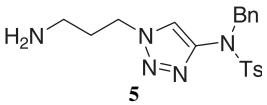
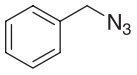
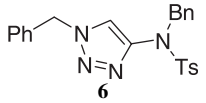
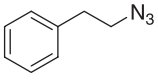
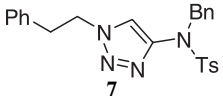
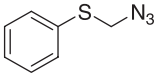
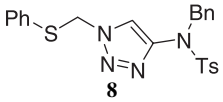
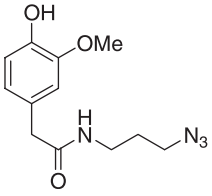
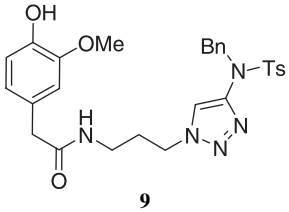
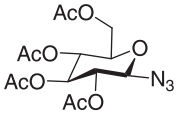
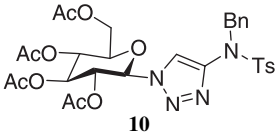
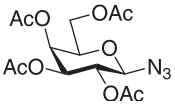
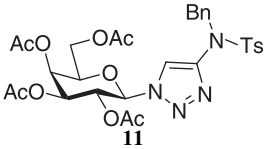
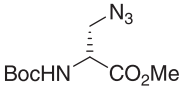
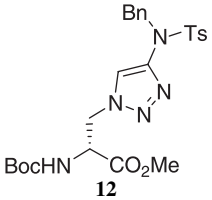
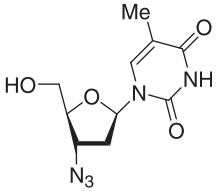
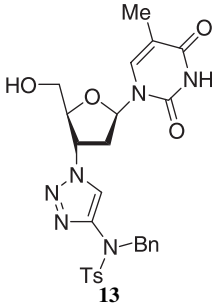
Although the complete mechanism of the 'click chemistry' has not been unambiguously elucidated,[22] it seems quite clear that the first step involves the formation of a copper acetylide. Since such a species has already been evoked in the Glaser[16] or Sonogashira couplings of ynamides,[17] we assume that the same intermediate can be postulated as the key reactive intermediate for the cycloaddition described here; hence the presence of a sulfonamide or carbamate protected amino group on the alkyne moiety does not alter the reactivity of the terminal alkyne in this synthetic transformation.

We should finally point out that there are many reports about the bioactivity of 4-amino imidazoles.[23] In search for potentially more active analogs, the most obvious transformation is the conversion of the imidazole ring into a triazole.[24] The synthetic protocol described in this paper should allow a quick and efficient access to such compounds.



Scheme 3. 'Click chemistry' of *N*-benzyl *N*-benzoyl ynamide.

Table 1. 'Click chemistry' of *N*-benzyl *N*-tosyl ynamide[a]

Entry	Azide	Product	Yield (%)
1		 **4**	58
2		 **5**	58
3		 **6**	38
4		 **7**	77
5		 **8**	68
6		 **9**	62
7		 **10**	96
8		 **11**	85
9		 **12**	43
10		 **13**	59

[a] For the exact conditions used in this reaction see the Section 4.

3. Conclusion

In conclusion, we have demonstrated that ynamides can be good partners for [3+2] cycloaddition affording a novel extension to the 'click chemistry' concept. Two ynamides bearing different protecting groups were successfully clicked with a wide range of azides. Starting from either very simple or highly functionalized azides afforded diversely 1-substituted 4-amino 1,2,3-triazoles. Further work is in progress to improve the yields of this reaction and to expand this approach to other ynamides.

4. Experimental

4.1. General considerations

Most of the azides used in the Huisgen cycloaddition described in this report are either commercially available and were used without further purification or were prepared according to standard protocols. Copper acetate[25] and sodium ascorbate were purchased from Aldrich. Reactions were run under air atmosphere and yields in Table 1 refer to isolated compounds (column chromatography) of greater than 95% purity as determined by ^{1}H NMR, the regiochemistry has been assigned based on the usually observed regioselectivity in similar click reactions. All new compounds were fully characterized by spectroscopic methods (^{1}H, ^{13}C NMR, MS, IR), HRMS.

4.1.1. *tert*-Butyl *N*-[2-(4-benzyl[(4-methylphenyl)sulfonyl]amino-1*H*-1,2,3-triazol-1-yl)ethyl] carbamate (4). To a stirred solution of **2** (100 mg, 0.35 mmol) and *N*-Boc 2-azido ethylamine (65 mg, 0.35 mmol) in ^{t}BuOH (2 mL) and $CHCl_3$ (0.3 mL) was added a premixed solution of $Cu(OAc)_2$ (13 mg, 70 μmol) and sodium ascorbate (30 mg, 0.14 mmol) in H_2O (5 mL). After vigorous stirring overnight the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Purification using flash chromatography (20% EtOAc in cyclohexane) afforded compound **4** as a white solid (95 mg, 0.20 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=8.0 Hz, 2H), 7.52 (s, 1H), 7.35 (d, J=7.6 Hz, 2H), 7.26–7.18 (m, 5H), 4.89 (s, 2H), 4.74 (br s, 1H), 4.35 (t, J=3.4 Hz, 2H), 3.51 (q, J=5.6 Hz, 2H), 2.45 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 144.0, 144.0, 135.8, 135.3, 129.7, 128.6, 128.3, 127.6, 127.4, 120.6, 80.0, 52.5, 50.2, 40.3, 28.2, 21.5; IR ν (cm^{-1}) 3396, 3154, 2978, 1712, 1550, 1514, 1360, 1167; MS (ESI): 416 (–^{t}Bu), 438 (–^{t}Bu+23), 494.

4.1.2. *N*1-[1-(3-Aminopropyl)-1*H*-1,2,3-triazol-4-yl]-*N*1-benzyl-4-methyl-1-benzenesulfonamide (5). Using the conditions as described before **2** (50 mg, 0.18 mmol) and a solution of 3-amino propylazide (0.80 mL, 2.2% in toluene) were combined. After purification using flash chromatography (2% MeOH in CH_2Cl_2) **5** (39 mg, 0.10 mmol, 58%) was obtained as a viscous oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.64 (d, J=8.2 Hz, 2H) 7.39–7.33 (m, 3H), 7.27–7.19 (m, 5H), 4.67 (s, 2H), 4.41 (t, J=6.0 Hz, 2H), 3.21 (t, J=5.7 Hz, 2H), 2.44 (s, 3H), 1.97 (p, J=5.7 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 144.1, 135.8, 129.3, 128.1, 127.9, 127.6, 127.3, 53.6, 43.7, 38.4, 20.6, 20.1; IR ν (cm^{-1}) 3393, 2975, 2515, 1729, 1630, 1453, 1339, 1289, 1161, 1091; MS (ESI): 385. HRMS (ESI-MS): for $C_{19}H_{22}N_5O_2S$ (M−1) calcd 384.1494, found 384.1468.

4.1.3. *N*1-Benzyl-*N*1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-4-methyl-1-benzenesulfonamide (6). Using the previously described conditions **2** (50 mg, 0.17 mmol) was combined with benzylazide (26 mg, 0.20 mmol). After further purification using flash chromatography (20% EtOAc in hexanes) **6** (27.4 mg, 66 μmol, 38%) was obtained as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J=8.4 Hz, 2H), 7.44 (s, 1H), 7.37–7.31 (m, 5H), 7.27–7.22 (m, 5H), 7.11–7.08 (m, 2H), 5.41 (s, 2H), 4.89 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 144.0, 135.7, 135.1, 134.2, 129.6, 129.0, 128.7, 128.6, 128.2, 127.6, 127.4, 120.1, 54.5, 52.5, 21.5; IR ν (cm^{-1}) 3138, 3034, 2954, 1753, 1552, 1341, 1164, 1089; MS (ESI): (M+23) 441. HRMS (ESI-MS): for $C_{23}H_{23}N_4O_2S$ (M+1) calcd 419.1542, found 419.1541.

4.1.4. *N*1-Benzyl-*N*1-(1-phenethyl-1*H*-1,2,3-triazol-4-yl)-4-methyl-1-benzenesulfonamide (7). Using the previously described conditions **2** (50 mg, 0.17 mmol) was combined with 2-azido ethyl benzene (29 mg, 0.20 mmol). After further purification using flash chromatography (20% EtOAc in hexanes) **7** (58.0 mg, 0.13 mmol, 77%) was obtained as a sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J=1.6, 8.4 Hz, 2H), 7.35–7.21 (m, 11H), 6.98–6.95 (m, 2H), 4.87 (s, 2H), 4.48 (t, J=7.1 Hz, 2H), 3.12 (t, J=7.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.5, 136.6, 135.8, 135.2, 129.6, 128.7, 128.6, 128.5, 125.3, 127.9, 127.7, 127.6, 127.3, 127.0, 120.5, 52.4, 52.0, 36.3, 21.5; IR ν (cm^{-1}) 3122, 3032, 2924, 1701, 1599, 1543; 1455, 1354, 1165; MS: (M+1) 433 (M+23) 455. HRMS (ESI-MS): for $C_{24}H_{25}N_4O_2S$ (M+1) calcd 433.1698, found 433.1683.

4.1.5. *N*1-Benzyl-*N*1-1-[(phenylsulfanyl)methyl]-1*H*-1,2,3-triazol-4-yl-4-methyl-1-benzenesulfonamide (8). Using the previously described conditions azidomethylsulfanyl benzene (140 mg, 0.85 mmol) was combined with **2** (361 mg, 1.27 mmol). Further purification (50% EtOAc in hexanes) yielded **8** as a yellowish oil (261 mg, 0.58 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.49 (d, J=8.0 Hz, 2H), 7.33–7.13 (m, 14H), 5.41 (s, 2H), 4.85 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 135.7, 135.0, 133.0, 131.1, 129.7, 129.4, 128.9, 128.6, 128.3, 127.7, 127.4, 120.0, 54.6, 52.5, 21.5; IR ν (cm^{-1}) 3650, 3296, 3154, 3063, 3032, 2926, 1754, 1676, 1598, 1553, 1454, 1355, 1225, 1165, 1091; MS: (M+23) 473. HRMS (ESI-MS): for $C_{23}H_{23}N_4O_2S_2$ (M+1) calcd 451.1262, found 451.1286.

4.1.6. *N*1-[3-(4-Benzyl[(4-methylphenyl)sulfonyl]amino-1*H*-1,2,3-triazol-1-yl)propyl]-2-(4-hydroxy-3-methoxyphenyl) acetamide (9). Using the previously described conditions, **2** (50 mg, 0.17 mmol) was combined in 48 h with *N*-(3-azidopropyl)-2-(4-hydroxy 3-methoxyphenyl) acetamide (45 mg, 0.17 mmol). After further purification using flash chromatography (gradient from 30 to 100% EtOAc in hexanes) **9** (59.4 mg, 0.11 mmol, 62%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.57 (d, J=8.2 Hz, 2H), 7.51 (s, 1H), 7.32 (d, J=7.0 Hz, 2H), 7.27–7.18 (m, 5H), 6.88 (d, J=7.9 Hz, 1H), 6.76 (s, 1H), 6.71 (d, J=7.9 Hz, 1H), 5.73 (br s, 1H), 4.86 (s, 2H), 4.19 (t, J=6.8 Hz, 2H), 3.86 (s, 3H), 3.44 (s, 2H), 3.09 (q, J=6.3 Hz, 2H), 2.41 (s, 3H), 1.98 (p, J=6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 146.9, 145.0, 144.1, 144.0, 135.7, 135.2, 129.7, 128.6, 128.3, 127.6, 127.3, 126.4, 122.0, 120.2, 114.8, 111.7, 55.9, 52.5, 48.0, 43.3, 36.3, 29.7, 21.5; IR ν (cm^{-1}) 3297, 2925, 1653, 1547, 1515, 1455, 1354, 1275, 1163; MS: (M+23) 572. HRMS (ESI-MS): for $C_{28}H_{32}N_5O_5S$ (M+1) calcd 550.2124, found 550.2159.

4.1.7. 1-{4-(Benzyl-toluene-4-sulfonyl)-amino-(1,2,3)-triazol-1-yl}-1-deoxy-β-D-glucopyranoside tetraacetate (10). Using the previously described conditions 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate (161 mg, 0.432 mol) and **2** (135 mg, 0.474 mol) were combined. Further purification using flash chromatography (50% EtOAc in cyclohexane) yielded a white solid (271.6 mg, 0.422 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.35 (d, J=7.6 Hz, 2H), 7.32–7.19 (m, 5H), 5.67 (d, J=8.4 Hz, 1H), 5.39–5.33 (m, 2H), 5.26 (t, J=8.4 Hz, 1H), 4.89 (s, 2H), 4.31 (dd, J=4.4, 12.4 Hz), 4.15 (d, J=13.2 Hz, 2H), 3.95 (d, J=10 Hz, 1H), 2.41 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.72 (s, 3H); IR ν (cm^{-1}) 3124, 2950, 1753, 1555, 1459, 1369, 1228, 1165, 1036; MS: (M+1) 659 (M+23) 681. HRMS (ESI-MS): for $C_{30}H_{34}N_4O_{11}NaS$ (M+23) calcd 681.1842, found 681.1868.

4.1.8. 1-{4-(Benzyl-toluene-4-sulfonyl)-amino-(1,2,3)-triazol-1-yl}-1-deoxy-β-D-galactopyranoside tetraacetate (11). Using the previously described conditions 1-azido-1-deoxy-β-D-galactopyranoside tetraacetate (250 mg, 0.777 mmol) was combined with **2** (331 mg, 1.16 mmol). After further purification using flash chromatography (50% EtOAc in hexanes) **11** (480 mg, 0.666 mmol, 85%) was obtained as a white fluffy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.59 (d, J=8.4 Hz, 2H) 7.35 (d, J=7.0 Hz, 2H), 7.28–7.18 (m, 5H), 5.67 (d, J=9.1 Hz, 1H), 5.52 (d, J=3.6 Hz, 1H), 5.49 (t, J=10.0 Hz, 1H), 5.21 (dd, J=3.6, 10.0 Hz, 1H), 4.90 (s, 2H), 4.18 (s, 1H), 4.21–4.08 (m, 2H), 2.41 (s, 3H), 2.24 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.0, 169.7, 168.5, 144.5, 144.0, 135.6, 135.0, 129.7, 128.6, 128.3, 127.6, 1274, 118.2, 86.8, 74.1, 70.5, 67.8, 66.7, 61.1, 52.1, 21.5, 20.6, 20.5, 20.4, 20.0; IR ν (cm^{-1}) 3646, 3487, 3152, 3033, 2940, 1757, 1677, 1557, 1458, 1370, 1224, 1166, 1092, 1061; MS: (M+23) 681. HRMS (ESI-MS): for $C_{30}H_{34}N_4O_{11}NaS$ (M+23) calcd 681.1842, found 681.1862.

4.1.9. Methyl 3-(4-benzyl[(4-methylphenyl)sulfonyl]-amino-1*H*-1,2,3-triazol-1-yl)-2*R*-[(*tert*-butoxycarbonyl)-amino] propanoate (12). Using the conditions as described before **2** (100 mg, 0.35 mmol) and (*R*)-2-Boc-amino-3-azido-propionic acid methyl ester (77 mg, 0.35 mmol) were combined. After further purification using a gradient from 20% EtOAc to 100% in hexane a white solid (77 mg, 43%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J=8.1 Hz, 2H), 7.48 (s, 1H), 7.34 (d, J=7.9 Hz, 2H), 7.29–7.21 (m, 5H), 5.22 (br d, J=7.0 Hz, 1H), 4.86 (dd, J=4.4, 18.4 Hz, 2H), 4.77–4.61 (m, 3H), 3.69 (s, 3H), 2.41 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 154.8, 144.0, 135.7, 135.0, 129.7, 128.7, 128.3, 127.6, 127.3, 121.3, 80.8, 65.7, 52.9, 52.4, 28.2, 21.5; IR ν (cm^{-1}) 3392, 1747, 1686, 1517, 1351, 1160; MS: (M+1) 530 (M+23) 552. HRMS (ESI-MS): for $C_{25}H_{32}N_5O_6S$ (M+1) calcd 530.2073, found 530.2078.

4.1.10. *N*1-Benzyl-*N*1-1-[2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-3-furanyl]-1*H*-1,2,3-triazol-4-yl-4-methyl-1-benzenesulfonamide (13). Using the conditions as previously described, AZT (40 mg, 0.15 mmol) and **2** (45 mg, 0.16 mmol) were combined. Further purification using flash chromatography (66% EtOAc in hexanes) resulted in a white solid (47.0 mg, 85 μmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.58 (d, J=8.2 Hz, 2H), 7.40 (s, 1H), 7.32 (d, J=6.7 Hz, 2H), 7.29–7.19 (m, 5H), 6.18 (t, J=6.5 Hz, 1H), 5.34–5.29 (m, 1H), 4.88 (s, 2H), 4.29–4.27 (m, 1H), 3.97–3.92 (m, 1H), 3.72–3.67 (m, 1H), 2.90–2.85 (m, 2H), 2.40 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 163.8, 150.4, 144.3, 137.6, 135.6, 135.1, 129.8, 128.5, 128.3, 127.7, 127.3, 119.8, 111.2, 88.2, 84.9, 61.3, 60.4, 59.5, 52.5, 37.3, 21.5, 20.9, 14.1, 12.3; IR ν 3443, 3126, 2927, 1713, 1683, 1545, 1469, 1357, 1275, 1165, 1092; MS: (M+1) 553, (M+23) 575. HRMS (ESI-MS): for $C_{26}H_{29}N_6O_6S$ (M+1) calcd 553.1869, found 553.1880.

4.1.11. *N*1-Benzyl-*N*1-1-[(phenylsulfanyl)methyl]-1*H*-1,2,3-triazol-4-yl benzamide (15). Using the previously described conditions **14** (50 mg, 0.17 mmol) was combined with azidomethylsulfanyl benzene (29 mg, 0.20 mmol). After further purification using flash chromatography (20% EtOAc in hexanes) **15** (46.5 mg, 11.6 μmol, 55%) was obtained as a sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J=7.1 Hz, 2H), 7.36–7.20 (m, 14H), 5.43 (br s, 2H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 136.9, 135.2, 132.4, 130.2, 129.4, 128.7, 128.4, 128.2, 127.9, 127.8, 127.4, 54.5, 52.0; IR ν (cm^{-1}) 3178, 3052, 1636, 1545, 1412, 1255, 1148, 973; MS: (M+23): 423. HRMS (ESI-MS): for $C_{23}H_{20}N_4ONaS$ (M+23) calcd 423.1256, found 423.1244.

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References and notes

1. (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489. (b) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037. (c) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (d) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**,

10, 1379. (e) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (f) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011. (g) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455.

2. Chechik-Lankin, E.; Livshin, S.; Marek, I. *Synlett* **2005**, *13*, 2098.
3. Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.
4. Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681.
5. Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727.
6. Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803.
7. Witulski, B.; Lumtscher, J.; Bergstrasser, U. *Synlett* **2003**, *5*, 708.
8. Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281.
9. (a) Witulski, B.; Gössmann, M. *Chem. Commun.* **1999**, 1879. (b) Witulski, B.; Gössmann, M. *Synlett* **2000**, *12*, 1793.
10. Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353.
11. (a) Witulski, B.; Buschmann, N.; Bergstrasser, U. *Tetrahedron* **2000**, *56*, 8473. (b) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511.
12. (a) Miniere, S.; Cintrat, J.-C. *Synthesis* **2001**, *5*, 705. (b) Miniere, S.; Cintrat, J.-C. *J. Org. Chem.* **2001**, *66*, 7385. (c) Timbart, L.; Cintrat, J.-C. *Chem. Eur. J.* **2002**, *8*, 1637. (d) Naud, S.; Cintrat, J.-C. *Synthesis* **2003**, *9*, 1391. (e) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095.
13. Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67.
14. Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509.
15. Rodriguez, D.; Castedo, L.; Saa, C. *Synlett* **2004**, *5*, 783.
16. Rodriguez, D.; Castedo, L.; Saa, C. *Synlett* **2004**, *2*, 377.
17. Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209.
18. Micetich, R. G.; Maiti, S. N.; Spevak, P.; Hall, T. W.; Yamabe, S.; Ishida, N.; Tanaka, M.; Yamazaki, T.; Nakai, A.; Ogawa, K. *J. Med. Chem.* **1987**, *8*, 1469.
19. (a) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
20. See for recent applications: (a) Helms, B.; Mynar, J. L.; Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15020. (b) Beatty, K. E.; Xie, F.; Wang, Q.; Tirrell, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 14150.
21. The Huisgen 1,3-dipolar cyclization between an azide and an ynamine has been reported but gave rise to the 1,5-substituted isomer. See: Humbert, G.; Schwickerath, W. *Liebigs Ann. Chem.* **1982**, *12*, 2105.
22. Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2210.
23. (a) Reigan, P.; Edwards, P. N.; Gbaj, A.; Cole, C.; Barry, S. T.; Page, K. M.; Ashton, S. E.; Luke, R. W. A.; Douglas, K. T.; Stratford, I. J.; Jaffar, M.; Bryce, R. A.; Freeman, S. *J. Med. Chem.* **2005**, *2*, 392. (b) Hu, W.; Burli, R. W.; Kaizerman, J. A.; Johnson, K. W.; Gross, M. I.; Iwamoto, M.; Jones, P.; Lofland, D.; Difuntorum, S.; Chen, H.; Bozdogan, B.; Appelbaum, P. C.; Moser, H. E. *J. Med. Chem.* **2004**, *18*, 4352.
24. Bertelli, L.; Biagi, G.; Calderone, V.; Giorgi, I.; Livi, O.; Scartoni, V.; Barili, P. L. *J. Heterocycl. Chem.* **2000**, *5*, 1169.
25. Although 'click chemistry' is mostly performed under copper sulphate catalysis we have experienced better results with copper acetate. See for similar findings in conjugate addition reaction of terminal alkynes: Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054.