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1-Protected 5-amido 1,2,3-triazoles via ruthenium-catalyzed [3+2] cycloaddition of azides and ynamides

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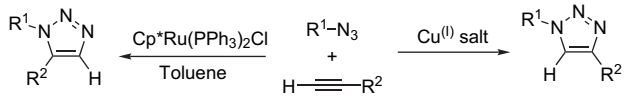
Abstract—Ynamides react with various azides in the ruthenium-catalyzed Huisgen [3+2] cycloaddition reaction. This ruthenium-catalyzed azide–ynamide cycloaddition reaction yields 1-protected 5-amido 1,2,3-triazoles.

1. Introduction

1,2,3-Triazoles have found many applications in the pharmaceutical and agricultural industries.[1] To obtain these heteroarenes, the most commonly used methodology involves the thermal 1,3-dipolar cycloaddition of azides with terminal alkynes. Nevertheless this reaction suffers from many drawbacks including the harsh conditions and the generation of a mixture of regioisomers.[2] Over the last decade, click chemistry[3] has emerged as a new concept and the copper-catalyzed Huisgen cycloaddition[4] has been one of the most prominent examples of this concept. Since then numerous applications of the [3+2] cycloaddition have been described in various fields such as bioconjugation and polymer science.[5] Whilst the copper-catalyzed cycloaddition yields the 1,4-isomers, use of a ruthenium complex affords the regioisomer, i.e., the 1,5-disubstituted triazole (see Scheme 1).[6]

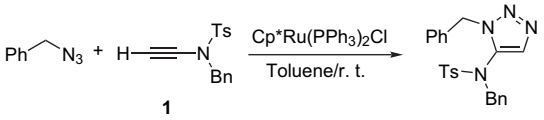


Scheme 1. Copper- and ruthenium-catalyzed Huisgen cycloaddition.

The copper-catalyzed approach is mostly restricted to the cycloaddition of terminal alkynes whereas the ruthenium catalyst allows the use of internal alkynes, the regioselectivity being mostly governed by the alkyne substitution pattern albeit no rationale has clearly emerged.[7] Despite their potential application, only a few 1,2,3-triazoles bearing a heteroatom at either the 4- or the 5-position have been synthesized.[8] To the best of our knowledge, examples are limited to halogens,[9] phosphorus,[10] silicon or tin,[11] sulfur or selenium[12] and oxygen.[13] Triazoles bearing an amino group are also of great interest,[14] they have been mainly synthesized from nitrile anions[15] or by cycloaddition of ynamines with activated azides[16] giving mixture of isomers or unstable compounds. We have recently reported the copper-catalyzed cycloaddition of ynamides with azides to furnish 4-amido 1,2,3-triazoles.[17] Following our initial report, Hsung described an elegant tandem azidination–[3+2] cycloaddition from ynamides.[18] We report here the ruthenium-catalyzed ynamide–organic azide cycloaddition to yield 5-amido 1,2,3-triazoles.

2. Results and discussion

The preliminary attempts were conducted with the reaction of *N*-benzyl, *N*-tosyl ynamide **1**[19] with benzyl azide. Surprisingly, the reaction proceeded very quickly and in less than 1 h all the starting material was consumed affording the 1,5-regioisomer as the sole compound as determined by ^{1}H NMR and LC/MS (Scheme 2).[20]



Scheme 2. Ruthenium-catalyzed Huisgen cycloaddition of **1** with benzyl-azide.

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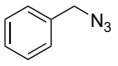
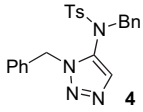
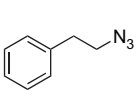
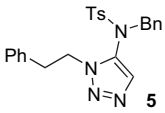
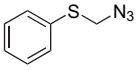
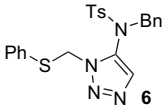
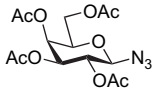
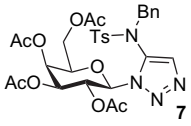
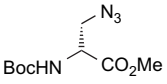
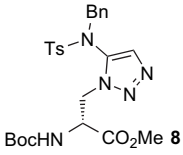
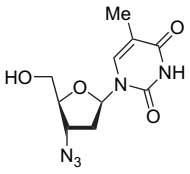
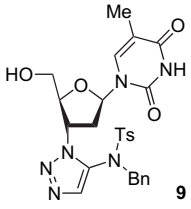
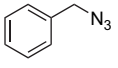
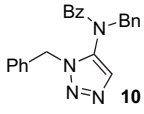
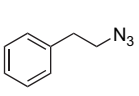
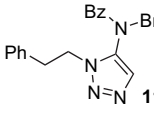
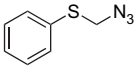
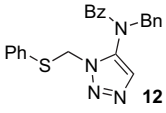
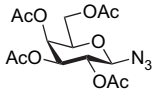
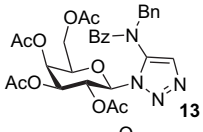
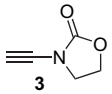
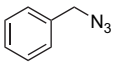
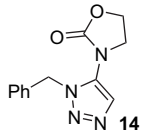
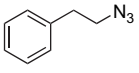
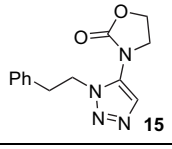
Table 1. Ruthenium-catalyzed Huisgen cycloaddition of ynamides[a]

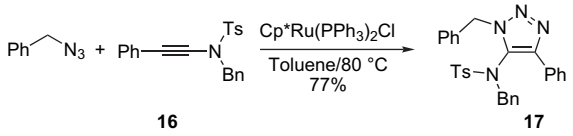
Entry	Ynamide	Azide	Triazole	Yield (%)
1	 **1**		 **4**	85[b]
2	**1**		 **5**	91[c]
3	**1**		 **6**	74[d]
4	**1**		 **7**	75[d]
5	**1**		 **8**	95[d]
6	**1**		 **9**	93[d]
7	 **2**		 **10**	92[d]
8	**2**		 **11**	89[d]
9	**2**		 **12**	70[d]
10	**2**		 **13**	65[d]
11	 **3**		 **14**	72[d]
12	**3**		 **15**	71[e]

[a] All reactions were run with 1 equiv of ynamide (1 mmol), 1.2 equiv of azide and 2.5 mol % of catalyst.
[b] Two hours, room temperature.
[c] Five hours, room temperature.
[d] Sixteen hours, 80 °C.
[e] Twenty-four hours, 80 °C.

We then investigated the reactions of **1** and other ynamides[19, 21] with a range of organic azides. The results are summarized in Table 1.

First it has to be stated that in all examples described in Table 1 only the 1,5-regioisomer is obtained. Even when the crude reaction mixture was difficult to analyze by NMR due to the occurrence of rotamers (entries 7–10), the LC/MS showed only one isomer. It is also noteworthy that the yields achieved were usually very high. Although the reaction rate was rapid for simple azides (entries 1–3), more sterically demanding azides required elevated temperatures and long reaction times to allow the reaction to proceed to completion. As already reported for the copper-catalyzed cycloaddition of ynamides, highly functionalized azides are suitable for this cycloaddition including carbohydrates (entries 4 and 10), aminoacids (entry 5) and AZT (entry 6). Finally although we were previously unsuccessful in reacting *N*-ethynyl 1,3-oxazolidinone **3** in the presence of copper, the ruthenium catalyst used here proved to be efficient for this substrate as well (entries 11 and 12).

It is noteworthy that the ruthenium catalyst allows the reaction of internal alkynes,[22] hence we decided to react ynamide **16** with benzyl azide (Scheme 3).



16 17

Scheme 3. Ruthenium-catalyzed Huisgen cycloaddition of internal ynamide with benzylazide.

The reaction was run overnight at 80 °C affording only one regioisomer. This regioisomer was assigned to structure **17** based on an X-ray diffraction analysis (see Fig. 1).

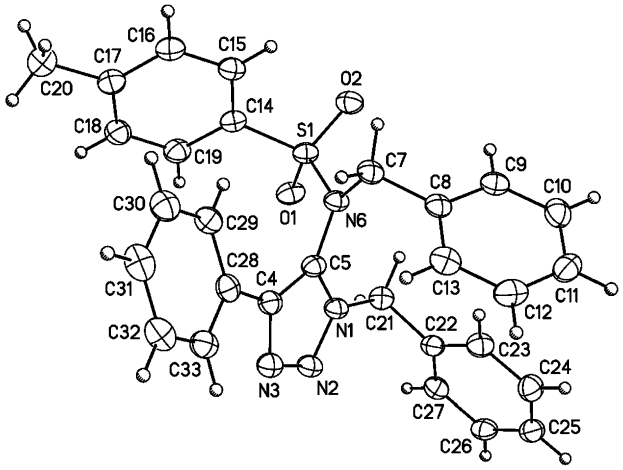


Figure 1. The crystal structure of **17**.

This result is in perfect agreement with the previously encountered regioselectivity when electron rich internal alkynes were used.[7]

3. Conclusion

We have shown that the ruthenium-catalyzed Huisgen cycloaddition of terminal ynamides is a general process affording the 1,5-disubstituted triazole isomer in good yields. This reaction proceeds under mild conditions to afford only one regioisomer. Even internal ynamides could be engaged in such reactions affording highly functionalized triazoles with complete regioselectivity.

4. Experimental section

4.1. General procedure for Cp*RuCl(PPh$_3$)$_2$ catalyzed cycloadditions

A mixture of azide (1.2 mmol, 1.2 equiv), ynamide (1 mmol) and Cp*RuCl(PPh$_3$)$_2$ (2.5 mol %) in anhydrous toluene (10–20 mL, 0.1–0.2 M in reactants) was stirred at a given temperature for a period of time indicated below Table 1. The progress of the reaction was monitored by TLC or LC/MS. In most cases the ynamide was completely consumed at the end of the reaction. The solvent was removed under vacuum and the product was purified by silica gel chromatography using a mixture of pentane/ethyl acetate or dichloromethane/methanol.

4.1.1. 1-Benzyl-5-(*N*-tosyl, *N*-benzyl)amino-1*H*-1,2,3-triazole (4). White solid, 173–174 °C; ^{1}H NMR (CDCl$_3$): δ 2.45 (s, 3H), 4.31 (s, 2H), 5.25 (s, 2H), 6.87–6.94 (t, 4H, J=7.6), 6.99 (s, 1H), 7.09–7.12 (t, 2H, J=7.4), 7.17–7.23 (m, 4H), 7.32 (d, 2H, J=8), 7.56 (d, 2H, J=8). ^{13}C NMR (CDCl$_3$): δ 21.9, 51.3, 56.4, 128.3, 128.4, 128.5, 128.8, 128.9, 129.5, 130.05, 130.12, 133.5, 133.7, 134.4, 134.8, 145.3. IR (KBr): 3132, 1597, 1545, 1495, 1448, 1349, 1165. EIMS: *m*/*z* 419 (100) [M+1], 837 (49) [2M+1], 859 (13) [2M+23], HRMS (ESI) calcd for $C_{23}H_{23}N_4O_2S$ (M+1): 419.1539; found: 419.1542.

4.1.2. 1-Phenethyl-5-(*N*-benzyl, *N*-tosylamino)-1*H*-1,2,3-triazole (5). White solid, amorphous; ^{1}H NMR (CDCl$_3$): δ 2.46 (s, 3H), 2.81 (br s, 2H), 4.2 (t, 2H, J=8.4), 4.44 (br s, 2H), 7.08 (s, 1H), 7.09–7.13 (m, 5H), 7.2–7.32 (m, 5H), 7.35 (d, 2H, J=8.1), 7.6 (d, 2H, J=8.1). ^{13}C NMR (CDCl$_3$): δ 21.6, 35.4, 48.2, 56.7, 126.8, 128.1, 128.6, 128.7, 128.9, 129.3, 129.9, 133.2, 133.9, 134.4, 137.4, 145.1. IR (KBr): 3120, 1598, 1544, 1495, 1453, 1351, 1170. ESIMS: *m*/*z* 433 (100) [M+1], 865 (22) [2M+1], HRMS (ESI) calcd for $C_{24}H_{25}N_4O_2S$ (M+1): 433.1679; found: 433.1698.

4.1.3. 1-Phenylsulfanylmethyl-5-(*N*-benzyl, *N*-tosylamino)-1*H*-1,2,3-triazole (6). White solid, 182–184 °C; ^{1}H NMR (CDCl$_3$): δ 2.47 (s, 3H), 4.54 (s, 2H), 5.51 (s, 2H), 6.97 (s, 1H), 7.11 (br d, 2H, J=5.3), 7.2–7.3 (m, 8H), 7.33 (d, 2H, J=7.8), 7.55 (d, 2H, J=7.8). ^{13}C NMR (CDCl$_3$): δ 21.8, 51.8, 56.5, 128.3, 128.4, 128.9, 128.9, 129.3, 129.8, 130.1, 130.7, 132.4, 133, 133.5, 133.8, 134.3, 145.3. IR (KBr): 3136, 1595, 1547, 1494, 1438, 1351, 1166. ESIMS: *m*/*z* 451 (98) [M+1], 473 (91) [M+23], 923 (100) [2M+23], HRMS (ESI) calcd for $C_{23}H_{22}N_4NaO_2S_2$ (M+23): 473.1065; found: 473.1082.

4.1.4. Acetic acid 4,5-diacetoxy-2-acetoxymethyl-6-[5-(*N*-benzyl, *N*-tosylamino)-[1,2,3]triazol-1-yl]-tetrahydro-pyran-3-yl ester (7). White solid, 75–78 °C; ^{1}H NMR (CDCl$_3$): δ 1.76 (br s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.07 (s, 3H), 2.48 (s, 3H), 3.65 (br d, 1H, J=7.7), 3.87 (br d, 1H, J=12.4), 4.11 (dd, 1H, J=4, J=12.4), 4.47 (m, 1H), 4.67 (m, 2H), 5.22 (td, 1H, J=1, J=9.9), 5.31 (t, 1H, J=9.4), 5.51 (d, 1H, J=9.4), 5.99 (td, J=1, J=9.4), 7.01 (s, 1H), 7.15–7.17 (m, 2H), 7.25–7.27 (m, 3H), 7.37 (d, 2H, J=7.8), 7.62 (d, 2H, J=7.8). ^{13}C NMR (CDCl$_3$): δ 20.4, 20.7, 20.8, 21.8, 57.1, 61.4, 67.7, 69.2, 73.7, 74.7, 81.6, 128.3, 128.9, 129, 129.2, 130.2, 130.4, 133.7, 134.4, 136.4, 145.6, 168.7, 169.4, 170.4, 170.7. IR (KBr): 1758, 1555, 1544, 1497, 1444, 1368, 1229. ESIMS: *m*/*z* 681 (100) [M+23], 1339 (86) [2M+23].

4.1.5. 3-{5-[*N*-Benzyl, *N*-tosylamino]-[1,2,3]triazol-1-yl}-2-*tert*-butoxycarbonylamino-propionic acid methyl ester (8). White solid, 56–58 °C; ^{1}H NMR (CDCl$_3$): δ 1.42 (s, 9H), 2.49 (s, 3H), 3.7 (s, 3H), 4.23 (dd, 1H, J=4, J=14), 4.38 (dd, 1H, J=6.4, J=14), 4.53 (br s, 2H), 4.6 (m, 1H), 5.31 (d, 1H, J=8.4), 7 (s, 1H), 7.09–7.12 (m, 2H), 7.23–7.3 (m, 3H), 7.37 (d, 2H, J=7.8), 7.61 (d, 2H, J=7.8). ^{13}C NMR (CDCl$_3$): δ 21.8, 28.4, 47.9, 52.5, 52.9, 56.9, 80.4, 128.3, 129.1, 129.4, 130.1, 130.1, 133.5, 133.8, 135.3, 145.4, 155.3, 170. IR (KBr): 3403, 1751, 1714, 1598, 1550, 1502, 1364, 1161. ESIMS: *m*/*z* 552 (69) [M+23], 568 (72) [M+39], 1081 (100) [2M+23], 1097 (23) [2M+39], HRMS (ESI) calcd for $C_{25}H_{32}N_5O_6S$ (M+1): 530.2072; found: 530.2073.

4.1.6. *N*-Benzyl-*N*-{3-[2-hydroxymethyl-5-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-tetrahydro-furan-3-yl]-3*H*-[1,2,3]triazol-4-yl}-4-methyl-benzenesulfonamide (9). White solid, decomposition; ^{1}H NMR (toluene-d_8, 340 K): δ 1.67 (s, 3H), 2.02 (s, 3H), 2.22 (m, 1H), 2.82 (m, 1H), 3.5 (m, 1H), 3.64 (d, 1H, J=12.1), 3.84 (m, 1H), 4.27 (s, 1H), 4.44 (m, 1H), 5.08 (td, 1H, J=4.6, J=8.7), 5.91 (t, 1H, J=6.6), 6.72 (s, 1H), 6.8–7 (m, 7H), 7.42 (d, 2H, J=8.2). ^{13}C NMR (CDCl$_3$): δ 12.5, 21.7, 38.1, 57, 61.3, 85.2, 87.9, 110.8, 128.1, 129, 129.1, 129.2, 129.3, 130.2, 132.7, 133.6, 134.8, 137.55, 145.6, 150.1, 143.7. IR (KBr): 3401, 1691, 1355, 1271, 1166, 1092. ESIMS: *m*/*z* 575 (47) [M+23], 1127 (100) [2M+23], HRMS (ESI) calcd for $C_{26}H_{28}N_6NaO_6S$ (M+23): 575.1682; found: 575.1689.

4.1.7. 1-Benzyl-5-(*N*-benzoyl, *N*-benzylamino)-1*H*-1,2,3-triazole (10). White solid, 110–111 °C; ^{1}H NMR (toluene-d_8, 340 K): δ 4.39 (br s, 2H), 4.69 (s, 2H), 6.78–7.01 (m, 12H), 7.06 (s, 2H), 7.12 (d, 2H, J=7.6). ^{13}C NMR (CDCl$_3$): δ 51.6, 52.9, 128, 128.1, 128.5, 128.6, 128.9, 129, 129.2, 131.3, 131.4, 133.7, 133.8, 135.9, 137.1, 169.7. IR (KBr): 2964, 1664, 1567, 1262, 1095, 1025. ESIMS: *m*/*z* 391 (100) [M+23], 759 (36) [2M+23], HRMS (ESI) calcd for $C_{23}H_{20}N_4NaO$ (M+23): 391.1546; found: 391.1535.

4.1.8. 1-Phenethyl-5-(*N*-benzoyl, *N*-benzylamino)-1*H*-1,2,3-triazole (11). Yellowish solid, amorphous; ^{1}H NMR (toluene-d_8, 340 K): δ 2.66 (t, 2H, J=7.6), 3.54 (t, 2H, J=7.6), 4.43 (br s, 2H), 6.75 (d, 2H, J=7.2), 6.79–7.06 (m, 12H), 7.17 (d, 2H, J=7.2). ^{13}C NMR (CDCl$_3$): δ 35.1, 48.2, 53.1, 127.1, 127.9, 128.3, 128.4, 128.7, 128.8, 128.8, 128.9, 130, 131.1, 133.7, 135.8, 137, 137.3, 169.4. IR (KBr): 3062, 1666, 1563, 1452, 1307. ESIMS: *m*/*z* 383 (100) [M+1], 405 (29) [M+23], 765 (31) [2M+1], 787 (47)

[2M+23], HRMS (ESI) calcd for $C_{24}H_{22}N_4NaO$ (M+23): 405.1683; found: 405.1691.

4.1.9. 1-Phenylsulfanylmethyl-5-(*N*-benzoyl, *N*-benzylamino)-1*H*-1,2,3-triazole (12). Brownish oil; ^{1}H NMR (toluene-d_8, 340 K): δ 4.72 (s, 2H), 4.99 (s, 2H), 6.86–7.29 (m, 16H). ^{13}C NMR ($CDCl_3$): δ 51.6, 53.2, 127.8, 128.3, 128.5, 128.6, 128.9, 129.4, 131, 131.2, 131.9, 132.2, 133.7, 135.9, 136.9, 169.6. IR (KBr): 1668, 1565, 1440, 1372, 1304, 1226. ESIMS: *m*/*z* 423 (100) [M+23], 823 (78) [2M+23], HRMS (ESI) calcd for $C_{23}H_{21}N_4OS$ (M+1): 401.1425; found: 401.1436.

4.1.10. Acetic acid 4,5-diacetoxy-2-acetoxymethyl-6-[5-(*N*-benzoyl-*N*-benzylamino)-[1,2,3]triazol-1-yl]-tetrahydro-pyran-3-yl ester (13). Brownish solid, 191–192 °C; ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 3H), 1.93 (s, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 3.82 (m, 1H), 4.13 (dd, 1H, *J*=5.8, *J*=12.5), 4.18 (dd, 1H, *J*=2.1, *J*=12.5), 5.22 (dd, 1H, *J*=9.6, *J*=9.9), 5.31 (br t, *J*=9.3), 5.53 (br d, 1H, *J*=9.4), 6.08 (br t, *J*=9.4), 6.84 (s, 1H), 7.2–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 20.5, 20.8, 62, 67.7, 69.2, 73.6, 75.3, 82, 128, 128.5, 128.7, 128.8, 129.1, 131.5, 132.2, 133.7, 135.8, 138.6, 168.2, 169.4, 170.5. IR (KBr): 1758, 1672, 1573, 1369, 1230. ESIMS: *m*/*z* 609 (15) [M+1], 631 (100) [M+23], 1217 (5) [2M+1], 1239 (34) [2M+23], HRMS (ESI) calcd for $C_{30}H_{32}N_4NaO_{10}$ (M+23): 631.1988; found: 631.2016.

4.1.11. 3-(1-Benzyl-1*H*-[1,2,3]triazol-5-yl)-oxazolidin-2-one (14). Brownish oil; ^{1}H NMR ($CDCl_3$): δ 3.28 (t, 2H, *J*=7.8), 4.13 (br t, 2H, *J*=7.8), 5.5 (s, 2H), 7.05–7.29 (m, 5H), 7.54 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 46.9, 52.6, 63, 127.5, 128.4, 128.5, 128.6, 129, 129.05, 131.8, 131.9, 132.7, 134.2, 155.2. IR (KBr): 1767, 1581, 1479, 1457, 1406, 1221. ESIMS: *m*/*z* 245 (100) [M+1], 267 (47) [M+23], 511 (79) [2M+23], HRMS (ESI) calcd for $C_{12}H1_2N_4NaO_2$ (M+23): 267.0859; found: 267.0858.

4.1.12. 3-(1-Phenethyl-1*H*-[1,2,3]triazol-5-yl)-oxazolidin-2-one (15). Yellow solid, 116 °C; ^{1}H NMR ($CDCl_3$): δ 3.23 (m, 4H), 4.3 (m, 2H), 4.57 (t, 2H, *J*=6.8), 7.04 (d, 2H, *J*=8), 7.24–7.28 (m, 3H), 7.46 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 36.7, 47.3, 50, 63.2, 127, 127.1, 128.9, 129.2, 132.3, 133.6, 138.1, 155.1. IR (KBr): 1758, 1579, 1403, 1217, 1141, 1104, 1034. ESIMS: *m*/*z* 259 [M+1], HRMS (ESI) calcd for $C_{13}H_{14}N_4NaO_2$ (M+23): 281.1010; found: 281.1014.

4.1.13. 1-Benzyl-4-phenyl-5-(*N*-benzyl, *N*-tosylamino)-1*H*-1,2,3-triazole (17). White solid, 178 °C; ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H), 4.26 (d, 1H, *J*=3.7), 4.87 (d, 1H, *J*=5.1), 4.95 (d, 1H, *J*=3.7), 5.23 (d, 1H, *J*=5.1), 6.95–7.27 (m, 17H), 7.66 (d, 2H, *J*=7). ^{13}C NMR ($CDCl_3$): δ 21.5, 51.4, 54.1, 126.6, 127.8, 128, 128.1, 128.4, 128.5, 128.7, 128.8, 129.4, 129.5, 130.1, 134.1, 134.2, 135.7, 141.7, 144.9. IR (KBr): 3060, 3034, 1595, 1555, 1493, 1454, 1359, 1167. ESIMS: *m*/*z* 495 (100) [M+1], 517 (11) [M+23], 1011 (8) [2M+23], HRMS (ESI) calcd for $C_{29}H_{26}N_4NaO_2S$ (M+23): 517.1688; found: 517.1674. Crystallographic data for the structure of compound **17** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 644158. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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