ORGANIC LETTERS

2010
Vol. 12, No. 20
4632−4635

General Solution to the Synthesis of *N*-2-Substituted 1,2,3-Triazoles

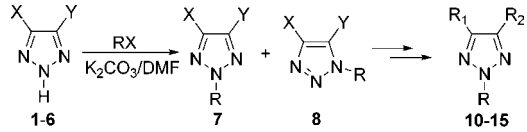
Xiao-jun Wang,*,† Li Zhang,† Dhileepkumar Krishnamurthy,† Chris H. Senanayake,† and Peter Wipf‡

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut 06877, United States, and Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

xiao-jun.wang@boehringer-ingelheim.com

Received August 18, 2010

ABSTRACT



1: X = Y = H, **2**: X = Y = Br, **3**: X = Y = I, **4**: X = Y = TMS,
5: X = Y = CO_2Me, **6**: X = Br, Y = TMS
with **2**: up to 92:8 of **7**:**8**
with **4**, **6**: up to 99:1 of **7**:**8**
10-**15:** R1 and R2 = H, alkyl, aryl

The regioselective N-alkylation of 1,2,3-triazoles 1−6 was studied. Good to excellent *N*-2 selectivity and high chemical yields for *N*-2-substituted 4,5-dibromotriazoles 7 were obtained with 4,5-dibromo- and 4-bromo-5-trimethylsilyl-1,2,3-triazoles. These building blocks can be readily converted to 2-mono-, 2,4-di-, and 2,4,5-polysubstituted triazoles 10−15, providing a general, protective, group-free method for the synthesis of *N*-2-substituted triazoles. Observed regioselectivities can be rationalized by a combination of Frontier Molecular Orbital, steric, and electrostatic directing effects on the heterocyclic scaffolds.

1,2,3-Triazoles have been known for over 100 years,[1] and they serve as important structural elements in many biologically active products.[2] Both thermal and Cu(I)/Ru(II)-catalyzed condensations of alkynes and azides provide an excellent approach to *N*-1/*N*-3-substituted triazoles.[3] However, there are no effective general methods for the synthesis of the complementary *N*-2-substituted regioisomers, although several unselective or specialized syntheses of *N*-2-substituted triazoles have been reported.[4,5] We recently disclosed a halogen-directed *N*-2 alkylation/arylation of bromo-substituted triazoles[6] and discovered that a combination of electronic and steric effects of the bromine substituent may contribute to the suppression of *N*-1/*N*-3 alkylation. To better understand these findings and establish a general strategy for access to *N*-2-substituted 1,2,3-triazoles, a systematic study on the alkylation of triazoles **1**−**6** with alkyl halides was conducted (Table 1) (Scheme 1).

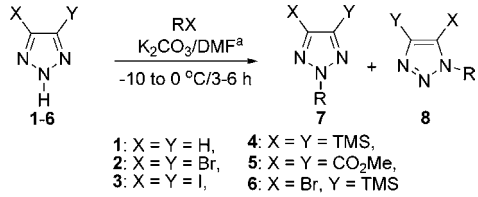
Dibromotriazole **2** was prepared by bromination of **1** with NBS (Scheme 1).[7] Surprisingly, diiodotriazole **3** could not be obtained by an analogous strategy. Fortunately, this compound was formed in good yield by treatment of *bis*(trimethylsilyl)triazole **4** with NIS.[8] Both **4** and the monotrimethylsilyltriazole **6** were accessed by Br/Mg exchange[9]

† Boehringer Ingelheim Pharmaceuticals Inc.
‡ University of Pittsburgh.

(1) Michael, A. *J. Prakt. Chem.* **1893**, *48*, 94–95.
(2) (a) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, p 669. (b) Dehne, H. In *Methoden der Organischen Chemie (Houben-Weyl)*; Schumann, E., Ed.; Thieme: Stuttgart, 1994; Vol. E8d, pp 305−405. (c) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137.
(3) (a) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984. (b) Kolb, H. C.; Fin, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (d) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7–17. (e) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930. (f) Tornø´e, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. Katritzky, A. R.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077–9079. (g) Majireck, M. M.; Weinreb, S. *J. Org. Chem.* **2006**, *71*, 8680–8683. (h) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.

10.1021/ol101965a
Published on Web 09/23/2010

Table 1. N-Alkylation of Triazoles **1**−**6**[a]



entry	triazoles	RX	ratio of **7**:**8**[b]	yield of (**7** + **8**)[c]
a	**1**	CH_3I	35:65	90
b	**1**	CH_3CH_2Br	48:52	92
c	**1**	MeO_2CCH_2Br	58:42	91
d	**2**	CH_3I	78:22	96
e	**2**	CH_3CH_2Br	87:13	95
f	**2**	MeO_2CCH_2Br	92:8	95
g	**2**	$PhCH_2CH_2Br$	90:10	93
h	**2**	*p*-$NCPhCH_2Br$	91:9	97
i	**2**	*m*-$MeOPhCH_2Br$	85:15	94
j	**2**	*p*-CF_3PhCH_2Br	92:8	95
k	**2**	3-$pyCH_2Br$	92:8	85
l	**3**	CH_3I	60:40	89
m	**3**	CH_3CH_2Br	74:26	93
n	**3**	MeO_2CH_2Br	78:22	96
o	**4**	CH_3I	76:24	85
p	**4**	CH_3CH_2Br	99:1	82
q	**4**	MeO_2CCH_2Br	99:1	88
r	**5**	CH_3I	50:50	91
s	**5**	CH_3CH_2Br	71:29	90
t	**5**	MeO_2CCH_2Br	73:27	88
u	**6**	CH_3I	73:21:5[d]	82
v	**6**	CH_3CH_2Br	94:4:<1[d]	89
w	**6**	MeO_2CCH_2Br	97:2:<1[d]	93
x	**6**	$PhCH_2CH_2Br$	>98:1:1[d]	88
y	**6**	*p*-$NCPhCH_2Br$	>98:1:1[d]	90

[a] See Table 2 for the screenings of solvents and reaction temperatures. [b] Ratio determined by proton NMR. [c] Both **7** and **8** were isolated by flash chromatography on silica gel. [d] Ratio of three regioisomers on *N*-2:*N*-3:*N*-1. The structures of two regioisomers on *N*-1 and *N*-3 were confirmed by two-dimetional NMR experiments.

of **2** after *in situ* protection of the NH group with TMSCl, followed by addition to TMSCl, as illustrated in Scheme 1.

Initially, we investigated the direct alkylation of **1** in DMF with three alkyl halides, i.e., methyl iodide, ethyl bromide,

Scheme 1. Preparation of Triazoles **2**−**6**

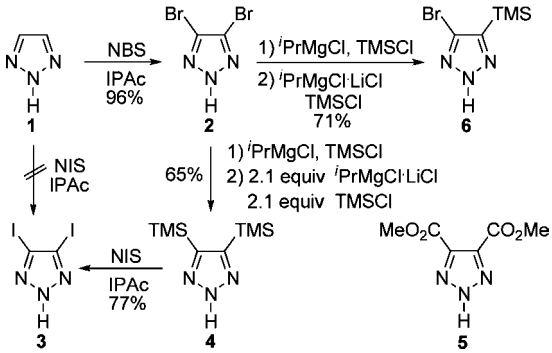
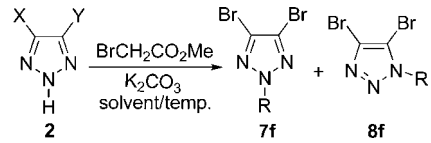


Table 2. Study of Solvent and Temperature Effects: *N*-2 Alkylation of **2** with Methyl α-Bromoacetate



entry	solvent	temp (°C)	time (h)	**7f**:**8f**[a]
1	THF	20	5	71:29
2	CH_3CN	20	2	80:20
3	CH_3COCH_3	20	2	80:20
4	CH_2Cl_2	20	5	n.r.[b]
5	MTBE	20	5	n.r.[b]
6	DMF	20	0.5	86:14
7	DMF	−10	5	92:8

[a] Ratio determined by both HPLC and proton NMR. [b] No product observed.

and methyl α-bromoacetate, using potassium carbonate as a base. The alkylation of **1** with these probe electrophiles was not regioselective, in agreement with previous accounts,[10] although an increase in *N*-2 selectivity was observed with the bulkier agents. These findings probably reflect that direct alkylations are subjected to Frontier Molecular Orbital (FMO) control and largely directed by the relative magnitude of the HOMO coefficients at the nitrogen atoms of the neutral 2*H*- and 1*H*-1,2,3-triazoles, which favor *N*-2 alkylation over *N*-1/*N*-3 (the latter having a statistical 2:1 advantage) (Figure 1). The orbital control is more pronounced with the more selective ethyl bromide and methyl α-bromoacetate.

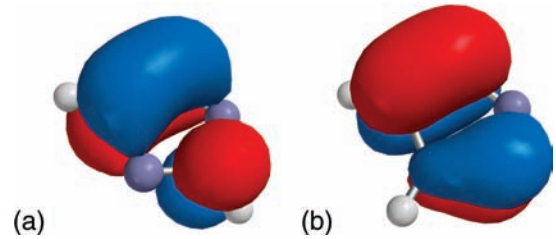


Figure 1. HOMO orbitals of 2*H*-triazole (a) and 1*H*-triazole (b).[11] The 2*H*-triazole tautomer predominates in most solvents.[12]

The alkylation of dibromotriazole **2** with ethyl bromide and methyl α-bromoacetate under the same reaction conditions produced the *N*-2 alkylated products **7e**−**h** and **8e**−**h** in up to 92:8 ratios (entries e−h, Table 1). A moderate *N*-2 selectivity was also observed with methyl iodide. While HOMO control remains important for directing incoming electrophiles in **2**, the steric bulk of the two bromine atoms acts in concert to disfavor *N*-1/*N*-3 alkylation (Figure 2).

Since 1,2,3-triazoles are quite NH-acidic (pK_a ~9.3), the alkylation in the presence of K_2CO_3 is likely to involve at least in part the anion of the heterocycle. Both the HOMO as well as the electrostatic potential distribution in the anion of **2** suggest

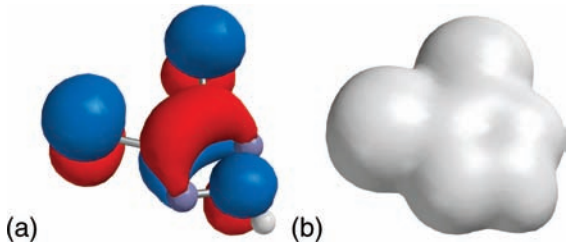


Figure 2. HOMO orbital (a) and electron density surface (b) of 2*H*-dibromotriazole **2**.[11]

high *N*-2 selectivity (Figure 3); accordingly, the electronic analysis of the anion is in agreement with the parent neutral system.

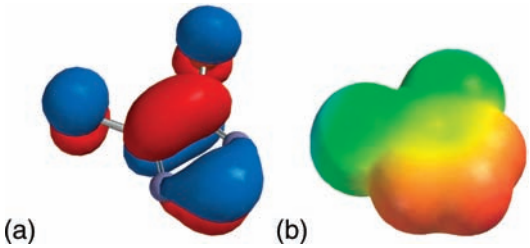


Figure 3. HOMO orbital (a) and electron density surfaces encoded with electrostatic potential (b) of the anion of 2*H*-dibromotriazole **2**.[11]

The alkylation of **2** with other alkyl halides than the three probe agents also produced *N*-2 alkylated triazoles in good to excellent regioselectivities and satisfactory yields (entries g−k, Table 1). In contrast, the *N*-2 regioselectivity for the alkylation of the diiodide **3** dropped off to moderate levels (entries l−n, Table 1). The *N*-1 alkylation of triazole **3** is slightly less sterically demanding, due to the longer C−I bonds at *C*-4 and *C*-5 (2.08 vs 1.88 Å for the C−Br bonds in **2**). Significantly, the partial charges (in e^-) at *N*-1/*N*-3 in the anion of diiodide **3** are calculated at −0.40, vs −0.16 at *N*-2. This electrostatic charge distribution favors *N*-1/*N*-3 alkylation in **3** to a greater extent than in the anion of dibromide **2**, which has partial charges of −0.38 and −0.18 at *N*-1/*N*-3 and *N*-2, respectively.

As expected, the alkylation of the sterically crowded bis-TMS triazole **4** with ethyl bromide and bromoacetate produced only *N*-2 products.[13] Methyliodide was again the least selective among these three alkylating agents (entries o−q, Table 1). Interestingly, the analogous direct alkylation of diester **5**, however, bearing two strongly electron-withdrawing carboxylate groups yielded a mixture of two regioisomers with much lower *N*-2 regioselectivity (entries r−t, Table 1).[14] A rationale for the erosion of regioselectivity with **5** can again be found in the consideration of the electrostatic charge distribution in the corresponding anion: The partial charges at *N*-1/*N*-3 are calculated at −0.42, vs −0.14 at *N*-2. The much greater negative partial charges at *N*-1/*N*-3 favor an electrostatic control of the alkylation process, opposing the FMO and steric effects.

We also investigated the alkylation of triazole **6** with an unsymmetrical 4,5-substitution pattern consisting of a bromo- and a sterically more demanding TMS group. This substitution pattern is synthetically valuable for the preparation of more diverse heterocyclic building blocks. While the alkylation of **6** with methyl iodide produced the *N*-2 alkylated **7u** and two other regioisomers (*N*-3 and *N*-1 isomers) in a ratio of 73:21:5 (entry u, Table 1), reactions with other halides proved significantly more regioselective. With ethyl bromide and α-bromoacetate, the ratio of **7**:**8** was improved to >94:4, and only a trace amount of the *N*-1 regioisomer was observed. Alkylation of **6** with phenethyl bromide and *p*-cyanobenzylbromide provided **7x**,**y** as sole products in excellent yields.

A brief examination of the effects of solvent[10b] and temperature for the alkylation of **2** using ethyl bromoacetate as the electrophile indicated that both exerted a significant influence on product regioselectivity (Table 2). The dipolar solvent DMF produced a record 92:8 selectivity for **7f** over **8f** at −10 °C.

The successful regioselective *N*-2 alkylation of triazoles provides an efficient approach toward a variety of differentially substituted heterocycles. As illustrated in Scheme 2, dibromotriazoles **7e** and **7g** were readily converted in

(4) (a) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171–3174. (b) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786–7787. (c) Chen, Y.; Liu, Y.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2008**, 3254–3256. (d) Iddon, B.; Nicholas, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1341–1347. (e) Kim, D. K.; Kim, J.; Park, H. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2401–2405. (f) Revesz, L.; Di Padova, F. E.; Buhl, T.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Wolf, R.; Zimmerlin, A. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2109–2112. Koren, A. O. *J. Heterocycl. Chem.* **2002**, *39*, 1111–1112.

(5) For examples on *N*-2 arylation, see: (a) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389–5392. (b) Lacerda, P. S. S.; Silva, A. M. G.; Tome, A. C.; Neves, M.; Silva, A. M. S.; Cavaleiro, J. A. S.; Llamas-Saiz, A. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 5487–5491. For examples on the *N*-2 alkylation, acetylation, or arylation of 5-arylated, 4-alkylated, or 4-acylated 1,2,3-triazoles, see: (c) Shi, X. US patent 2010/0069644 A1.

(6) (a) Wang, X.-H.; Zhang, Li.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5026–5028. (b) Wang, X.-J.; Sidhu, K.; Zhang, Li.; Campbell, S.; Haddad, N.; Reeves, D. C.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5490–5493.

(7) Iddon, B.; Nicholas, M. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1341–1347.

(8) (a) Hosomi, A.; Iijima, S.; Sakurai, H. *Chem. Lett.* **1981**, 243–246. (b) Dichloro-1,2,3-triazole could not be prepared either by treatment of **1** with NCS or by the treatment of **5** with NCS.

(9) For halogen−metal exchange with ^{i}PrMgCl·LiCl, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302–4320.

(10) For examples, see: (a) Ohta, S.; Kawasaki, I.; Uemura, T.; Yamashita, M.; Yoshioka, T.; Yamaguchi, S. *Chem. Pharm. Bull.* **1997**, *45*, 1140–1145. (b) Begtrup, M.; Larsen, P. *Acta Chem. Scand.* **1990**, *44*, 1050–1057.

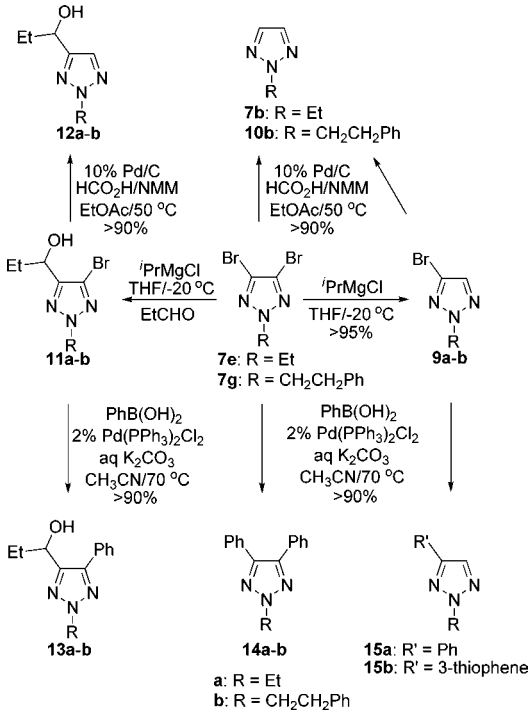
(11) *Spartan 08*, v.1.21; Wavefunction, Inc.: Irvine, CAwas used; all calculations were performed at the RB3LYP/6-311G* level.

(12) Albert, A.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1903–1905.

(13) For regioselective *N*-2 glycosylation and hydroxyformylation, see: (a) Sanghvi, Y. S.; Bhattacharya, B. K.; Kini, G. D.; Matsumoto, S. S.; Larson, S. B.; Jolley, W. B.; Robins, R. K.; Revankar, G. R. *J. Med. Chem.* **1990**, *33*, 336–344. (b) See ref.4a

(14) For nonregioselective examples, see: Tom, A. C. In *Sciences of Synthesis*; Storr, R. C., Gilchrist, T. L., Eds.; Thieme: Stuttgart, NY, 2004; Vol. 13, p 415.

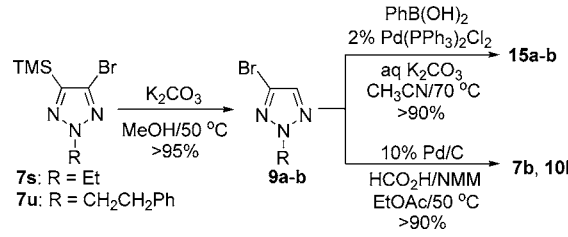
Scheme 2. Synthesis of *N*-2-Substituted 1,2,3-Triazoles from Building Blocks



excellent yields to monobromides **9a**,**b** by a Br/Mg exchange. The subsequent Suzuki cross-coupling of **9a**,**b** with boronic acids produced high yields of 2,4-disubstituted triazoles **15a**,**b**, which could not be prepared efficiently otherwise.[15] 2,4-Disubstituted triazoles **12a**,**b** were formed by hydrogenation of **11a**,**b** derived from the Br/Mg exchange of **7e** and **7g** followed by addition to propanaldehyde. 2,4,5-Trisubstituted triazoles **13a**,**b** and **14a**,**b** were obtained in excellent

(15) (a) De Meijere, A., Diederich, F., Eds. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004 (b) *Handbook of Organopalladium Chemistry*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002.

Scheme 3. Alternative Syntheses of *N*-2-Substituted 1,2,3-Triazoles



Furthermore, triazoles **7s** and **7u** were readily transformed into the same products **9a**,**b** by treatment with K_2CO_3 in MeOH, and both were converted to 2,4-disubstituted triazoles **15a**,**b** in the same fashion as mentioned above. Hydrogenation of **9a**,**b** produced the *N*-2 monosubstituted triazoles **7b** and **10b** (Scheme 3). With the available methodologies for C−C bond formation by cross-coupling of bromides and by manipulating the functionality of the bromo- and TMS substituents, many different kinds of polysubstituted 1,2,3-triazoles are now synthetically accessible.[15]

In summary, we have performed a systematic study on the direct N-alkylation of triazoles, avoiding the use of protective groups. Good to excellent *N*-2 regioselectivities were obtained with 4,5-dibromo-, 4-bromo-5-trimethylsilyl-, and 4,5-bis(trimethylsilyl)-1,2,3-triazoles. Product formation can be rationalized by a combination of FMO, steric, and electrostatic directing effects on the heterocyclic scaffolds. Together with our previous studies,[6] these new protocols establish a convenient and versatile strategy for the synthesis of *N*-2-substituted 1,2,3-triazoles.

Supporting Information Available: Spectroscopic data and copies of $^1H/^{13}C$ NMR spectra for compounds **3**−**6**, **7**, **8**, and **9**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101965A