Organic LETTERS

Letter

pubs.acs.org/OrgLett

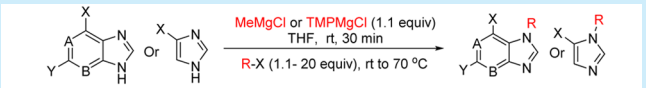
Direct, Regioselective *N*-Alkylation of 1,3-Azoles

Shuai Chen,* Russell F. Graceffa,* and Alessandro A. Boezio

Medicinal Chemsitry Department, Amgen, Inc., 360 Binney Street, Cambridge, Massachusetts 02142, United States

Supporting Information

ABSTRACT: Regioselective *N*-alkylation of 1,3-azoles is a valuable transformation. Organomagnesium reagents were discovered to be competent bases to affect regioselective alkylation of various 1,3-azoles. Counterintuitively, substitution selectively occurred at the more sterically hindered nitrogen atom. Numerous examples are provided, on varying 1,3-azole scaffolds, with yields ranging from 25 to 95%.



25-95% isolated yield, 34 examples, single step, protecting-group free

The concept of protecting-group-free (PGF) synthesis has gained prominence in the synthetic organic chemistry community over the past decade.[1] A successful PGF synthesis of a target molecule is advantageous for a number of reasons; it eliminates time-consuming and tedious manipulation of protecting groups and increases efficiency with respect to atom economy, loss of material, waste production, and synthetic design.[2]

Numerous biologically interesting natural products and medicinally important small molecules contain 1,3-azoles (e.g., imidazole, benzimidazole, imidazopyridine, and purine) (Figure 1). One challenge for the synthesis of 1,3-azole-containing molecules is the ambident nature of the azole toward *N*-alkylation chemistry.[3] A particularly challenging situation arises when the more sterically hindered nitrogen of the unsymmetrical azole is the target for alkylation. Under conventional conditions, alkylation favors the less sterically encumbered site.[4] In many instances, the desired reverse selectivity could be achieved through protection of the less hindered position followed by alkylation of the desired position and then deprotection.[5,6] A PGF alternative to this less efficient process would therefore be desirable.

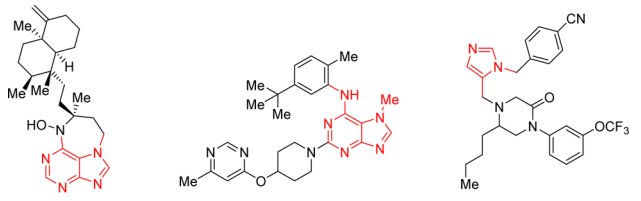
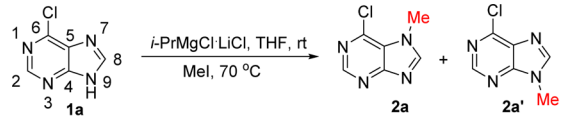


Figure 1. Selected examples of natural and biologically active compounds that contain 1,3-azoles.

Recently, a large quantity of N^7-methyl-6-chloropurine (**2a**) was required as an intermediate toward the scale-up of a medicinal chemistry lead for in vivo studies.[7] Unfortunately, the only method known for the production of **2a** utilized a strategy that relied upon a reduction/oxidation as well as a protection/deprotection process, which was nonideal for the preparation of large quantities of material.[5g] In order to facilitate the rapid synthesis of **2a**, conditions to reverse the inherent selectivity for alkylation of the N^9 over the N^7 position were investigated. It was discovered that deprotonation of 6-chloropurine with *i*-PrMgCl·LiCl followed by alkylation with methyl iodide furnished the desired regioisomer with 9:1 selectivity (**2a**/**2a**′) in 70% yield. Using this unoptimized method, 30 g of **2a** was prepared in a single reaction (Scheme 1).[8]

Scheme 1. Chemoselective Methylation of 6-Chloropurine



30g scale, **2a**:**2a'**= 9:1, 70% yield

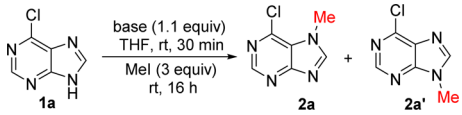
A thorough literature search revealed that the selective alkylation of the more hindered position of 1,3-azoles was uncommon. The only examples of direct N^7 alkylation of purine utilized a cobalt complex as a transient protecting group.[9] However, difficult access to the cobalt complexes, long reaction times, and a narrow substrate scope limit the potential applications for this method. Due to the lack of literature precedent for direct regioselective alkylation of the more hindered position of 1,3-azoles, we decided to investigate this transformation more rigorously.

Starting from our original conditions (Scheme 1), optimization was directed toward maximizing selectivity and conversion. A range of various bases including organomagnesium, organozinc, and lithium reagents were examined in the methylation of 6-chloropurine in THF at room temperature.[10] *i*-PrMgCl·LiCl and *s*-BuMgCl·LiCl gave similar N^7/N^9 selectivity (25:1 and 26:1, respectively) with a slightly higher conversion in the former case (Table 1, entries 1 and 2). Use of the non-nucleophilic Knochel–Hauser base TMPMgCl·LiCl (2,2,6,6-tetramethylpiperidinylmagnesium lithium chloride complex) resulted in lower selectivity with fair conversion (entry 3). Interestingly, use of *i*-

Received: October 15, 2015

DOI: 10.1021/acs.orglett.5b02994
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Base Screen for the Methylation of 6-Chloropurine



entry	base	conv[a] (%)	2a:2a'[b]
1	*i*-PrMgCl·LiCl	64	25:1
2	*s*-BuMgCl·LiCl	50	26:1
3	TMPMgCl·LiCl	50	15:1
4	*i*-PrMgCl	65	>99:1
5	MeMgCl	73	>99:1
6	MeMgBr	<5	21:1
7	MeMgI	<5	20:1
8	TMPMgCl	65	72:1

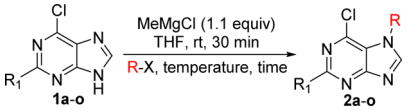
[a]Conversion determined by LC−MS. [b]Product ratio determined by ^{1}H NMR spectroscopy.

PrMgCl without LiCl complexation improved the N^7/N^9 selectivity to >99:1, with good conversion at ambient temperature (entry 4). Encouraged by this result, MeMgCl was tested and provided similar selectivity and improved yield in this transformation (entry 5). Interestingly, when the counterion of the Grignard reagent was changed from chloride to bromide or iodide, the conversion and the selectivity dramatically decreased (entries 6 and 7). Additionally, TMPMgCl could be employed in this method, with good selectivity (entry 8).[11,12] The non-nucleophilic nature of this base, relative to MeMgCl, allows for application of this strategy in the presence of sensitive functional groups.[13,14]

After MeMgCl was identified as the optimal base, alkylation of 6-chloropurine with a variety of alkylating reagents was studied (Table 2, entries 1−9). As anticipated, the N^7-substituted regioisomer was obtained irrespective of the aliphatic alkylating reagent employed in this transformation. Alkylation using unactivated electrophiles was sluggish even at elevated temperatures and with excess alkylating reagent. For example, *n*-butyl iodide required refluxing temperatures for 3 days to deliver a 25% yield of alkylated material (entry 4). The product selectivity was diminished with more reactive electrophiles. Decreased N^7 selectivity was observed for phenacyl bromide at room temperature; however, the product ratio could be improved (N^7/N^9 = 5:1) through slow addition of phenacyl bromide to the reaction mixture at low temperature (entry 9). The present conditions were also found to be amenable to the regioselective alkylation of 2,6-dichloropurine, a common building block used in medicinal chemistry (entries 10−15).[3b] A small amount of N^9-substituted products were observed in these cases (<10% detected by ^{1}H NMR analysis of reaction mixtures) albeit in good to excellent isolated yields for the N^7-regioisomer (72−90%).

To understand whether the selectivity in this transformation was a result of electronic or steric effects, purine derivatives with various substituents at the C^6 position were investigated (Table 3). TMPMgCl was utilized for the alkylation of 6-bromopurine

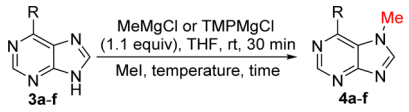
Table 2. Alkylation of 6-Chloropurine and 2,6-Dichloropurine



entry	2	R^1	alkylating reagent (equiv)	temp (°C)	time (h)	yield[a] (%)
1	**a**	H	MeI (3.0)	50	5	95
2	**b**	H	EtI (3.0)	70	16	81
3	**c**	H	*n*-PrI (20.0)	70	16	85
4	**d**	H	*n*-BuI (20.0)	70	72	25
5	**e**	H	BnBr (3.0)	50	20	88
6	**f**	H	CH_2=$CHCH_2Br$ (20.0)	70	16	90
7	**g**	H	$CH{\equiv}CCH_2Br$ (3.0)	70	16	72
8	**h**	H	$CF_3CH_2SO_3CF_3$ (2.0)	70	16	82
9[b]	**i**	H	$C_6H_5COCH_2Br$ (1.1)	−78 to rt	8	69
10	**j**	Cl	MeI (3.0)	50	16	90
11	**k**	Cl	EtI (3.0)	70	16	72
12	**l**	Cl	BnBr (3.0)	70	16	77
13	**m**	Cl	CH_2=$CHCH_2Br$ (3.0)	70	16	74
14	**n**	Cl	$CH{\equiv}CCH_2Br$ (3.0)	70	16	81
15	**o**	Cl	$CF_3CH_2SO_3CF_3$ (2.0)	70	16	74

[a]Isolated yield of the desired regioisomer.[15] [b]See text for details.

Table 3. Methylation of Purine Derivatives



entry	4	R	MeI (equiv)	temp (°C)	time (h)	yield[a] (%)
1	**a**	NMe_2[b]	10.0	25	16	25[d]
2	**b**	OMe[b]	10.0	25	22	57[d]
3	**c**	SMe[b]	3.0	70	16	80
4	**d**	Me[b]	3.0	70	30	77
5	**e**	Br[c]	3.0	25	20	80
6	**f**	CN[c]	1.5	70	24	78

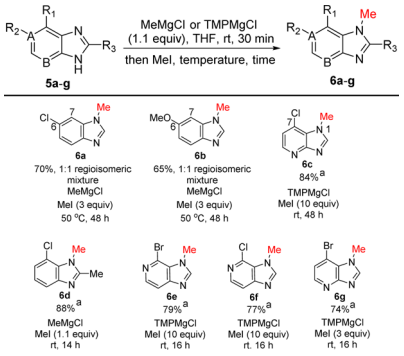
[a]Isolated yield of desired regioisomer.[15] [b]MeMgCl as the base. [c]TMPMgCl as the base. [d]Overmethylation of desired prouduct caused reduced yield in these reactions.

and 6-cyanopurine at room temperature. The use of MeMgCl as a base for these substates resulted in the formation of dehalogenated and methyl addition byproducts (entries 5 and 6). While selectivity was not affected by the electronic nature of the substituent on the purine, the yields were influenced by the electronic nature of the substituent at the C^6 position (entries 1 and 2). These observations suggest that steric effects govern the selectivity in this transformation with respect to this substitution pattern.

Gratifyingly, this method could also be effectively applied to various other bicyclic 1,3-azoles (Scheme 2). The methylation of 4-chloro-2-methyl-1*H*-benzo[*d*]imidazole gave the more sterically hindered regioisomeric product **6d** in 88% yield. 7-Substituted 1*H*-imidazo[4,5-*b*]pyridines provided the desired N^1-methylated products in good yields (**6c** and **6g**). Similarly, 4-substituted-3*H*-imidazo[4,5-*c*]pyridine afforded the desired N^3-methylation under standard conditions (**6e** and **6f**). However, a benzimidazole substrate with a chloride (EWG) or methoxide (EDG) at C^6 rather than at the C^7 position provided a 1:1 ratio of regioisomeric products (**6a**−**b**). In order to reduce the steric component, we moved the substituent to a remote position (C^6). If the regiochemistry was influenced by electronics, we would expect to observe some selectivity; however, the electronic character of the substituent had no effect on the regiochemistry of the products. This observation provides further evidence that

DOI: 10.1021/acs.orglett.5b02994
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Methylation of 1,3-Azoles[a]

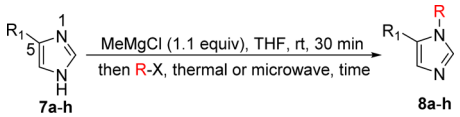


[a]Isolated yield of desired regioisomer.[15]

the alkylation is dictated by steric effects rather than by electronics. In addition, the presence and position of a nitrogen atom in the 6-membered ring does not affect the regioselectivity of 1,3-azole methylation. However, a C^7 substituent adjacent to the site of alkylation is required to differentiate the steric environment of the two reactive nitrogen atoms in the 1,3-azole ring.

Encouraged by the excellent selectivity of various bicyclic 1,3-azoles, we set out to extend this methodology to the alkylation of unsymmetrical imidazoles. To our delight, the expected N^1 substituted imidazole was the major product under standard reaction conditions (Table 4). Bromide and cyano groups were

Table 4. Alkylation of Imidazoles



entry	8	R_1	alkylating reagent (equiv)	base	temp (°C)	time (h)	yield[b] (%)
1	a	Ph	MeI (1.1)	MeMgCl	25	48	76
2	b	*t*-Bu	MeI (1.1)	MeMgCl	25	48	87
3	c	Me	MeI (1.5)	MeMgCl	70	20	64
4	d	Cl	MeI (1.5)	MeMgCl	70	20	69
5	e	Br	MeI (1.5)	TMPMgCl	70	20	69
6	f	CN	MeI (1.5)	TMPMgCl	70	20	74
7[a]	g	Ph	CH_2=$CHCH_2Br$ (1.5)	MeMgCl	120	2	42
8[a]	h	Ph	CH≡CCH_2Br (1.1)	MeMgCl	70	10	35

[a]Microwave irradiation. [b]Isolated yield of desired regioisomer.[15]

tolerated using TMPMgCl as the base and afforded a good yield of the N^1 regioisomeric products (entries 5 and 6). Electrophiles other than methyl iodide showed poor reactivity at ambient temperature (Table 4, entries 7 and 8).[15,16]

In conclusion, the direct, protecting-group free alkylation of the more sterically encumbered position of a wide range of 1,3-azoles has been demonstrated. High yields and regioselectivity were achieved using commercially available alkylmagnesium reagents or easily prepared TMPMgCl. It was observed that selectivity was not affected by the electronic nature of the substituents on the purine; however, the yields were influenced by the electronic character of the substituents. This transformation may also be useful for the simplified preparation of 1,3-azole-containing biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02994.

Synthetic methods, analytical methods, condition opimization, and full characterization of materials (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: schen@fc-cdci.com.
*E-mail: russellg@amgen.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Paul Krolikowski (Amgen) for 2D NMR (HSQC, HMBC, ROSEY) structure confirmations.

■ REFERENCES

(1) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193−205.
(2) Hoffmann, R. W. *Synthesis* **2006**, *20*, 3531−3541.
(3) (a) Pappo, D.; Shimony, S.; Kashman, Y. *J. Org. Chem.* **2005**, *70*, 199−206. (b) Rivkin, A.; Ahearn, S. P.; Chichetti, S. M.; Hamblett, C. L. Y.; Garcia, Y.; Martinez, M.; Hubbs, J. L.; Reutershan, M. H.; Daniels, M. H.; Siliphaivanh, P.; Otte, K. M.; Li, C.; Rosenau, A.; Surdi, L. M.; Jung, J.; Hughes, B. L.; Crispino, J. L.; Nikov, G. N.; Middleton, R. E.; Moxham, C. M.; Szewczak, A. A.; Shah, S.; Moy, L. Y.; Kenific, C. M.; Tanga, F.; Cruz, J. C.; Andrade, P.; Angagaw, M. H.; Shomer, N. H.; Miller, T.; Munoz, B.; Shearman, M. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2279−2282. (c) Williams, T. M.; Bergman, J. M.; Brashear, K.; Breslin, M. J.; Dinsmore, C. J.; Hutchinson, J. H.; MacTough, S. C.; Stump, C. A.; Wei, D. D.; Zartman, C. B.; Bogusky, M. J.; Culberson, J. C.; Buser-Doepner, C.; Davide, J.; Greenberg, I. B.; Hamilton, K. A.; Koblan, K. S.; Kohl, N. E.; Liu, D.; Lobell, R. B.; Mosser, S. D.; O'Neill, T. J.; Rands, E.; Schaber, M. D.; Wilson, F.; Senderak, E.; Motzel, S. L.; Gibbs, J. B.; Graham, S. L.; Heimbrook, D. C.; Hartman, G. D.; Oliff, A. I.; Huff, J. R. *J. Med. Chem.* **1999**, *42*, 3779−3784.
(4) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell: New York, 2010; pp 416−538.
(5) For purine alkylation, see: (a) Singh, D.; Wani, M. J.; Kumar, A. *J. Org. Chem.* **1999**, *64*, 4665−4668. (b) Pappo, D.; Kashman, Y. *Tetrahedron* **2003**, *59*, 6493−6501. (c) Jähne, G.; Kroha, H.; Müller, A.; Helsberg, M.; Winkler, I.; Gross, G.; Scholl, T. *Angew. Chem.* **1994**, *106*, 603−605; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 562−563. (d) Hakimelahi, G. H.; Ly, T. W.; Moosavi-Movahedi, A. A.; Jain, M. L.; Zakerinia, M.; Davari, H.; Mei, H. C.; Sambaiah, T.; Moshfegh, A. A.; Hakimelahi, S. *J. Med. Chem.* **2001**, *44*, 3710−3720. (e) Lebraud, H.; Cano, C.; Carbain, B.; Hardcastle, I. R.; Harrington, R. W.; Griffin, R. J.; Golding, B. T. *Org. Biomol. Chem.* **2013**, *11*, 1874−1878. (f) Kohda, K.; Baba, K.; Kawazoe, Y. *Tetrahedron Lett.* **1987**, *28*, 6285−6288. (g) Kotek, V.; Chudíková, N.; Tobrman, T.; Dvořák, D. *Org. Lett.* **2010**, *12*, 5724−5727. (h) Van Den Berge, E.; Robiette, R. *J. Org. Chem.* **2013**, *78*, 12220−12223.
(6) For imidazole alkylation, see: (a) Roumen, L.; Peeters, J. W.; Emmen, J. M. A.; Beugels, I. P. E.; Custers, E. M. G.; de Gooyer, M.; Plate, R.; Pieterse, K.; Hilbers, P. A. J.; Smits, J. F. M.; Vekemans, J. A. J.; Leysen, D.; Ottenheijm, H. C. J.; Janssen, H. M.; Hermans, J. J. R. *J. Med. Chem.* **2010**, *53*, 1712−1725. (b) Kumar, S.; Jaller, D.; Patel, B.; LaLonde, J. M.; DuHadaway, J. B.; Malachowski, W. P.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem.* **2008**, *51*, 4968−4977.
(7) (a) Schenkel, L.; Identification of a selective TRPA1 antagonist that demonstrates potent in vivo inhibition. *Abstracts of Papers, 247th ACS*

DOI: 10.1021/acs.orglett.5b02994
Org. Lett. XXXX, XXX, XXX−XXX

National Meeting & Exposition, Dallas, TX, Mar 16−20, 2014; American Chemical Society, Washington, DC, 2014; p MEDI-177. (b) Unpublished results.

(8) Small-batch chromotography was needed to purify the product. The NMR of product matches literature value. Okamura, T.; Kikuchi, T.; Fukushi, K.; Arano, Y.; Irie, T. *Bioorg. Med. Chem.* **2007**, *15*, 3127−3133 For a detailed procedure of the large-scale synthesis of **2a**, see the Supporting Information..

(9) (a) Ono, Y.; Izawa, Y.; Fu, Z.-H. *J. Chem. Soc., Chem. Commun.* **1995**, *1*, 9. (b) Marzilli, L. G.; Epps, L. A.; Sorrell, T.; Kistenmacher, T. J. *J. Am. Chem. Soc.* **1975**, *97*, 3351−3358. (c) Dalby, C.; Bleasdale, C.; Clegg, W.; Elsegood, M. R. J.; Golding, B. T.; Griffin, R. J. *Angew. Chem.* **1993**, *105*, 1822−1823; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1696−1697. (d) Kashima, C.; Harada, Y.; Hosomi, A. *Heterocycles* **1993**, *35*, 433−436.

(10) Organolithium and organozinc reagents were investigated. Organolithium bases showed higher conversions but lower selectivities compared to organomagnesium bases at room temperature. A range of ethereal solvents was investigated. THF resulted in the best conversion and regioselectivity. For more details, see the Supporting Information.

(11) Hauser, C. R.; Walker, H. G., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 295−297.

(12) Schlecker, W.; Huth, A.; Ottow, E. *J. Org. Chem.* **1995**, *60*, 8414−8416.

(13) Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016−8018.

(14) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414−8416.

(15) The identification of the regiochemistry was determined by the use of ^{1}H, ^{13}C, HSQC, and HMBC spectra. There exists clear evidence in the long-range ^{1}H−^{13}C HMBC data as to what side of the molecule the methyl group has added. The carbon chemical shifts of the two bridge carbons are quite distinct from each other. We were able to use the long-range ^{1}H−^{13}C HMBC data to correlate the methyl protons to each of the bridge carbons and determine connectivities. Therefore, the regiochemistry of methylation could be determined (see the Supporting Information, for example).

(16) Attempts to accelerate the reaction rate with excess alkylating reagent or elevated temperature led to the formation of undesired overalkylated imidazolium salts.

DOI: 10.1021/acs.orglett.5b02994
Org. Lett. XXXX, XXX, XXX−XXX