Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 2065

www.rsc.org/obc

COMMUNICATION

Microwave promoted C6-alkylation of purines through S_NAr-based reaction of 6-chloropurines with 3-alkyl-acetylacetone†

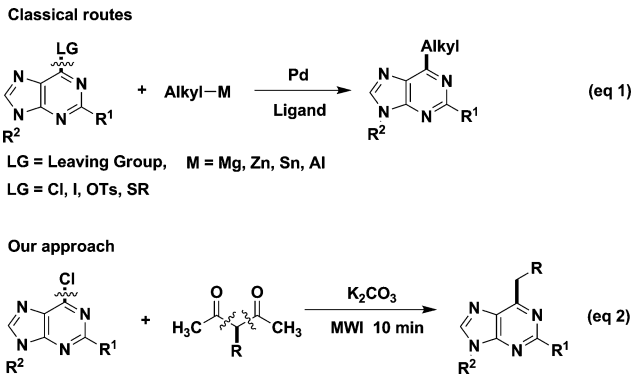
Hai-Ming Guo,*[a] Yu Zhang,[a] Hong-Ying Niu,[b] Dong-Chao Wang,[a] Zhi-Liang Chu[a] and Gui-Rong Qu*[a]

Received 20th December 2010, Accepted 25th January 2011
DOI: 10.1039/c0ob01213k

C6-Alkylated purine analogues were obtained in good to excellent isolated yields by S_NAr reaction of 6-chloropurine derivatives with 3-alkyl-acetylacetone. 3-Alkyl-acetylacetones were employed as alkylating agents and C6-alkylated purines were obtained highly selectively within short reaction time under microwave irradiation conditions. This work is complementary to the classical coupling reactions for the synthesis of C6-alkylated purine analogues.

The biological activities of C6 modified purine derivatives span a wide range from antiviral and antineoplastic to hypertensive.[1] In particular, C6-alkylated purine analogues or other (hetero)aryl derivatives possess a broad spectrum of biological effects such as cytostatic,[2] antiviral[3] and antimicrobial activities[4] or receptor modulation.[5] For example, 6-methylpurine and its ribonucleoside have highly cytotoxic[6] and antitumor activities.[7] So it is not surprising that the preparation of these purine derivatives has received considerable attention lately.

The most common method for the synthesis of C6-alkylated purines is transition metal catalyzed cross coupling reaction of C6-substituted purines and alkyl organometallics (eq 1, Scheme 1). In this respect, Suzuki-,[8] Stille-,[9] Negishi-,[10] and Kumada-[11] coupling reactions have all been exploited successfully, and various organometallic reagents[12] are involved. Hana Dvořáková *et al.* synthesized these compounds *via* a secondary or tertiary Grignard reagent with 6-chloropurines.[13] Michal Hocek *et al.* reported the synthesis of these compounds *via* Pd-catalyzed cross-couplings of 6-chloropurines with Reformatsky reagent in the presence of ligands.[14] 6-Methylpurine derivatives were prepared by Pd-catalyzed cross-couplings of 6-chloropurines with methylzinc bromide[15] or trimethylaluminium.[16] Other 6-alkylpurines were also prepared by Ni-, Fe-, or Cu- catalyzed couplings of 6-halo or 6-methylsulfanylpurines with Grignard reagents.[17] However, these methods employed either noble metal catalysts or alkyl organometallic reagents under rigorous reaction conditions such as anhydrous and nitrogen atmosphere.



Scheme 1 Different routes for the synthesis of C6-alkylated purines.

We have recently reported the reactions of 6-halopurines with ethyl acetoacetate to yield 2-(purin-6-yl)acetoacetic acid ethyl esters, (purin-6-yl)acetates and 6-methylpurines under different reaction conditions.[18] So we predicted that 3-alkyl-acetylacetone could also be a kind of alkylating agent. Up until now, there has been no report on the synthesis of alkylated purines, heterocycles, or arenes using alkyl-acetylacetones as alkylating agents. On the basis of our research interest toward the modification of purines,[19] herein, we describe new results concerning the synthesis of C6-alkylpurine analogues through a microwave-promoted S_NAr reaction of 6-chloropurine derivatives with 3-alkyl-acetylacetone (eq 2, Scheme 1). For the first time, 3-alkyl-acetylacetones were used as alkylating agents, thus avoiding the use of organometallics and noble metal catalysts.

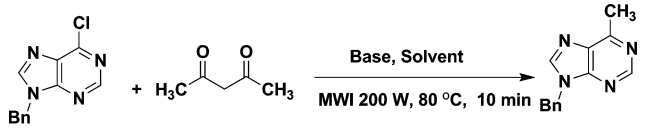
We began our investigation by examining the microwave promoted nucleophilic substitution reaction between 9-benzyl-6-chloropurine **1**, and acetylacetone **2** in the presence of various solvents (Table 1, entries 1–4). The results showed that DMSO was the best solvent for the reaction. In DMSO, the desired product 9-benzyl-6-methyl purine **3** was obtained in 89% yield at 80 °C in the presence of 7.5 equiv of K_2CO_3 for 10 min (entry 4). Next, we examined the effect of base on the yields of 9-benzyl-6-methyl purine **3**. No product was obtained when the reaction was conducted without any base (entry 5). It was evident that anhydrous K_2CO_3 was the most effective base for this transformation compared with the other investigated bases (entries 7–8). Changing the amount of K_2CO_3 showed that 7.5

[a]*College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang 453007, Henan, China. E-mail: guohm518@hotmail.com, quguir@sina.com; Fax: +86 373 3329276; Tel: +86 373 3329255*

[b]*School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang 453003, China*

† Electronic supplementary information (ESI) available: General information, experimental procedures, and characterization data for the products including spectroscopic information. See DOI: 10.1039/c0ob01213k

Table 1 Microwave promoted nucleophilic substitution reaction of 9-benzyl-6-chloropurine **1** with acetylacetone **2**[a]



Entry	Solvent	Temp. (°C)	Base (7.5 eq)	Time (min)	Yield (%)[b]
1	THF	65	K_2CO_3	10	*NR*[c]
2	CH_2Cl_2	40	K_2CO_3	10	*NR*[c]
3	DMF	80	K_2CO_3	10	10
4	**DMSO**	**80**	**K_2CO_3**	**10**	**89**
5	DMSO	80	No base	10	*NR*[c]
6	DMSO	80	K_2CO_3[d]	10	88
7	DMSO	80	Na_2CO_3	10	68
8	DMSO	80	Cs_2CO_3	10	72
9	DMSO	80	K_2CO_3	5	52
10	DMSO	80	K_2CO_3	15	90
11	DMSO	60	K_2CO_3	10	66
12	DMSO	100	K_2CO_3	10	88

[a] *Reagents and conditions*: 0.5 mmol **1**, 2.5 mmol acetylacetone **2** in 2 mL solvent for the indicated time, 7.5 equiv base and MWI (200 W). [b] Isolated yields based on purines. [c] NR = no reaction. [d] 8.5 eq K_2CO_3.

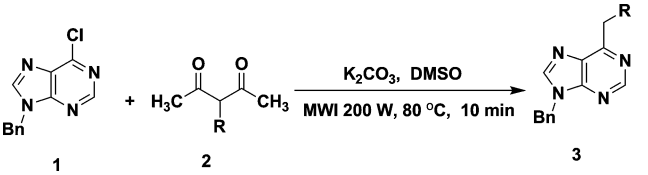
equiv of K_2CO_3 was the best choice (entries 4 and 6). Irradiation time had some influence on the yields (entries 9–10); it seemed that the reaction reached chemical equilibrium after being irradiated for 10 min. When the reaction time was longer than 10 min, the yield remained almost unchanged (entries 4 and 10), therefore 10 min was the optimized reaction time. Further screening of the reaction temperature (entries 11–12) confirmed that 80 °C was the best choice.

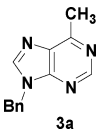
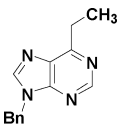
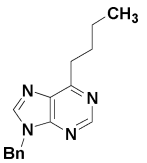
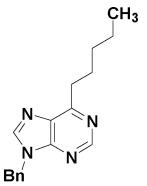
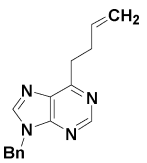
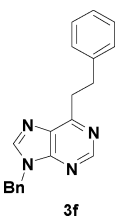
Under the optimized reaction conditions, the scope and generality of the reaction with a series of 3-alkyl-acetylacetones were explored. As shown in Table 2, the yield of the product became lower from 89% to 52% when the R group became gradually longer (entries 1–4). Also, 3-allyl- and 3-benzyl-acetylacetone gave moderate yield (entries 5 and 6). In general, the reaction proceeded smoothly for various substituted acetylacetone to produce the desired 9-benzyl-6-alkylated purines.

Naturally, after the development of various 3-alkyl-acetylacetones, we further explored the alkylation of various N9-substituted purine analogues, including purine nucleosides. As shown in Table 3, when the H atom on N9 was substituted by an alkyl group, good yields were obtained (entries 1–2, 4–5). And to our delight, the reactions starting from acyclic nucleoside (entry 3) and protected nucleoside (entry 6) gave 92% and 62% yields, respectively. Unfortunately, when active hydrogen occurred on the N9 position of purine, no desired product was obtained (entries 7–8).

Finally, direct alkylation using various active methylene compounds such as β-diketone, β-keto ester and β-diester with 9-benzyl-6-chloropurine was examined. The results are summarized in Table 4. The reaction proceeded smoothly for β-diketone and β-keto ester to give C6-methylated products within a short time (entries 1–3). However, β-diester gave a low yield because the decarboxylation reaction was difficult when two ester groups occurred on the substrate **2** (entry 4).

Table 2 Microwave promoted nucleophilic substitution reaction of 9-benzyl-6-chloropurine **1** with 3-alkyl-acetylacetones **2**[a]

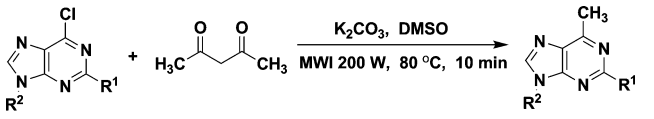


Entry	R	Product	Yield (%)[b]
1	H	 **3a**	89
2	CH_3	 **3b**	82
3	*n*-Pr	 **3c**	68(80)[c]
4	*n*-Bu	 **3d**	52(76)[c]
5		 **3e**	72
6	Bn	 **3f**	76

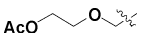
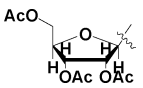
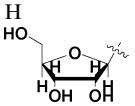
[a] *Reagents and conditions*: 0.5 mmol **1**, 2.5 mmol **2**, 3.75 mmol K_2CO_3 in 2 mL DMSO and MWI 200 W (80 °C) for 10 min. [b] Isolated yields based on purines. [c] The yields in parentheses were obtained after 20 min.

In conclusion, this work describes a new S_NAr based reaction between 6-chloropurines and 3-alkyl-acetylacetones under microwave irradiation. The application of 3-alkyl-acetylacetones as alkylating agents allows the reaction to be carried out under

Table 3 Microwave promoted nucleophilic substitution reaction of 6-chloropurine derivatives **1** with acetylacetone **2**[a]

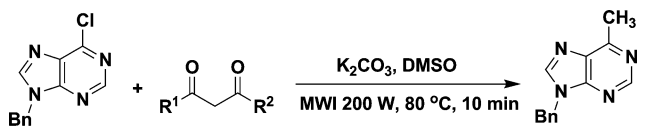


1 2 3

Entry	R^1	R^2	Product	Yield (%)[b]
1	H		**3a**	89
2	H		**3g**	76
3	H		**3h**	92
4	H		**3i**	88
5	Cl		**3j**	87
6	Cl		**3k**	62[c]
7	H	H	**3l**	0
8	H		**3m**	0

[a] *Reagents and conditions*: 0.5 mmol 6-chloropurine derivatives **1**, 2.5 mmol acetylacetone **2**, 3.75 mmol K_2CO_3 in 2 mL DMSO and MWI 200 W (80 °C) for 10 min. [b] Isolated yields based on purines. [c] The reaction time was 4 min.

Table 4 Microwave promoted nucleophilic substitution reaction of 9-benzyl-6-chloropurine **1** with various active methylene compounds **2**[a]



1 2 3a

Entry	R^1	R^2	Yield (%)[b]
1	CH_3	CH_3	89
2	CH_3	CH_3CH_2O	85
3	CH_3CH_2	CH_3CH_2O	82
4	CH_3CH_2O	CH_3CH_2O	32

[a] *Reagents and conditions*: 0.5 mmol 9-benzyl-6-chloropurine **1**, 2.5 mmol methylene compound **2**, 3.75 mmol K_2CO_3 in 2 mL DMSO and MWI 200 W (80 °C) for 10 min. [b] Isolated yields based on purines.

mild reaction conditions without the use of noble metal catalyst, organometallic reagent, or complex ligand and offers a simple, efficient, and more environmentally begin approach for the preparation of C6-alkylated purines. This methodology is more attractive than the previously reported methods due to the simplicity of the procedure, the absence of expensive catalyst and ligand, short reaction time, the generality of the reaction, and generally satisfactory yields. This work opens an effective new route for modification at C6 of purines and is complementary to the classical coupling reactions for synthesis of C6-alkylated purine analogues.

Acknowledgements

We are grateful for financial support from the National Nature Science Foundation of China (Grant Nos. 20772024, 20802016, and 21072047), the Program for New Century Excellent Talents in University of Ministry of Education (NCET-09-0122), the Program for Innovative Research Team in University of Henan Province (2008IRTSTHN002), and the Henan Nature Science Foundation (102300410253).

Notes and references

1 (*a*) L. Havlíček, J. HanuŠ, J. Veselý, S. Leclerc, L. Meijer, G. Shaw and M. Strnad, *J. Med. Chem.*, 1997, **40**, 408; (*b*) L. J. S. Knutsen, J. Lau, H. Petersen, C. Thomsen, J. U. Weis, M. Shalmi, M. E. Judge, A. Jon Hansen and M. J. Sheardown, *J. Med. Chem.*, 1999, **42**, 3463; (*c*) T. Tobrman and D. Dvořák, *Org. Lett.*, 2006, **8**, 1291.
2 (*a*) M. Hocek, A. Holý, I. Votruba and H. Dvořáková, *J. Med. Chem.*, 2000, **43**, 1817; (*b*) M. Hocek, A. Holý, I. Votruba and H. Dvořáková, *Collect. Czech. Chem. Commun.*, 2001, **66**, 483.
3 M. Hocek, P. Nauš, R. Pohl, I. Votruba, P. A. Furman, P. M. Tharnish and M. J. Otto, *J. Med. Chem.*, 2005, **48**, 5869.
4 (*a*) A. K. Bakkesteun, L.-L. Gundersen, G. Langli, F. Liu and J. M. J. Nolsøe, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1207; (*b*) G. Andersen, L.-L. Gundersen, J. Nissen-Meyer, F. Rise and B. Spilsberg, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 567; (*c*) L.-L. Gundersen, J. Nissen-Meyer and D. Spilsberg, *J. Med. Chem.*, 2002, **45**, 1383; (*d*) A. K. Bakkestuen, L.-L. Gundersen and B. T. Utenova, *J. Med. Chem.*, 2005, **48**, 2710; (*e*) M. Brændvang and L.-L. Gundersen, *Bioorg. Med. Chem.*, 2005, **13**, 6360; (*f*) M. Brændvang and L.-L. Gundersen, *Bioorg. Med. Chem.*, 2007, **15**, 7144.
5 (*a*) A. J. Cocuzza, D. R. Chidester, S. Culp, L. Fitzgerald and P. Gilligan, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1063; (*b*) L. C. W. Chang, R. F. Spanjersberg, J. K. von Frijtag Drabbe Kunzel, T. Mulder-Krieger, J. Brussee and A. P. Ijzerman, *J. Med. Chem.*, 2006, **49**, 2861.
6 J. A. Montgomery and K. Hewson, *J. Med. Chem.*, 1968, **11**, 48.
7 D. A. Clarke, F. S. Philips, S. S. Sternberg and C. C. Stock, *Ann. N. Y. Acad. Sci.*, 1954, **60**, 235.
8 M. Havelková, D. Dvořák and M. Hocek, *Synthesis*, 2001, (11), 1704.
9 L. L. Gundersen, *Tetrahedron Lett.*, 1994, **35**, 3155.
10 (*a*) M. Hocek, D. Hocková and H. Dvořáková, *Synthesis*, 2004, **6**, 889; (*b*) M. Hocek, I. Votruba and H. Dvořáková, *Tetrahedron*, 2003, **59**, 607; (*c*) A. Bråthe, G. Andresen, L.-L. Gundersen, K. E. Malterud and F. Rise, *Bioorg. Med. Chem.*, 2002, **10**, 1581.
11 A. Fürstner, A. Leitner, M. Méndez and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856.
12 (*a*) M. Hocek, *Eur. J. Org. Chem.*, 2003, 245; (*b*) L. A. Agrofoglio, I. Gillaizeau and Y. Saito, *Chem. Rev.*, 2003, **103**, 1875.
13 H. Dvoráková, D. Dvorák and A. Holý, *Tetrahedron Lett.*, 1996, **37**, 1285.
14 Z. Hasník, P. Šilhár and M. Hocek, *Tetrahedron Lett.*, 2007, **48**, 5589.
15 (*a*) M. Hocek and H. Dvoráková, *J. Org. Chem.*, 2003, **68**, 5773; (*b*) A. E. A. Hassan, R. A. I. Abou-elkair, J. A. Montgomery and J. A. Secrist III, *Nucleosides, Nucleotides Nucleic Acids*, 2000, **19**, 1123.
16 (*a*) I. Èerňa, R. Pohl, B. Klepetáøová and M. Hocek, *Org. Lett.*, 2006, **8**, 5389; (*b*) M. Hocek, R. Pohl and I. Císařová, *Eur. J. Org. Chem.*, 2005, 3026; (*c*) P. Šilhár, R. Pohl, I. Votruba, B. Klepetářová and M. Hocek, *Collect. Czech. Chem. Commun.*, 2006, **71**, 788.
17 (*a*) D. E. Bergstrom and P. A. Reddy, *Tetrahedron Lett.*, 1982, **23**, 4191; (*b*) K. G. Estep, K. A. Josef, E. R. Bacon, P. M. Carabates, S. Rumney, G. M. Pilling, D. S. Krafte, W. A. Volberg, K. Dillon, N. Dugrenier, G. M. Briggs, P. C. Canniff, W. P. Gorczyca, G. P. Stankus and A. M. Ezrin, *J. Med. Chem.*, 1995, **38**, 2582; (*c*) M. Hocek, D. Hocková and H.

Dvořáková, *Synthesis*, 2004, 889; (*d*) M. Hocek and R. Pohl, *Synthesis*, 2004, 2869.
18 G. R. Qu, Z. J. Mao, H. Y. Niu, D. C. Wang, C. Xia and H. M. Guo, *Org. Lett.*, 2009, **11**, 1745.
19 (*a*) H. M. Guo, P. Li, H. Y. Niu, D. C. Wang and G. R. Qu, *J. Org. Chem.*, 2010, **75**, 6016; (*b*) H. M. Guo, Y. Y. Wu, H. Y. Niu, D. C. Wang and G. R. Qu, *J. Org. Chem.*, 2010, **75**, 3863; (*c*) G. R. Qu, R. Xia, X. N. Yang, J. G. Li, D. C. Wang and H. M. Guo, *J. Org. Chem.*, 2008, **73**, 2416; (*d*) G. R. Qu, B. Ren, H. Y. Niu, Z. J. Mao and H. M. Guo, *J. Org. Chem.*, 2008, **73**, 2450; (*e*) G. R. Qu, J. Wu, Y. Y. Wu, F. Zhang and H. M. Guo, *Green Chem.*, 2009, **11**, 760; (*f*) G. R. Qu, L. Zhao, D. C. Wang, J. Wu and H. M. Guo, *Green Chem.*, 2008, **10**, 287; (*g*) H. M. Guo, J. Wu, H. Y. Niu, D. C. Wang, F. Zhang and G. R. Qu, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3098.

