ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 6, pp. 874–878. © Pleiades Publishing, Ltd., 2019.

A Convenient Synthesis of N^2-Alkylated Guanines

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Received December 20, 2018; revised December 25, 2018; accepted December 29, 2018

Abstract—An improved three-step synthesis of N^2-alkylated guanines has been developed starting from N^2-Boc-protected 2-amino-6-chloropurine which was treated with Boc_2O, and the resulting doubly N^2,9-protected derivative was subjected to N^2-alkylation with alkyl halides, followed by hydrolysis. The advantages of this procedure include short reaction steps, simple operations, and good yields.

Keywords: guanine, N^2-alkylation, Boc protection.

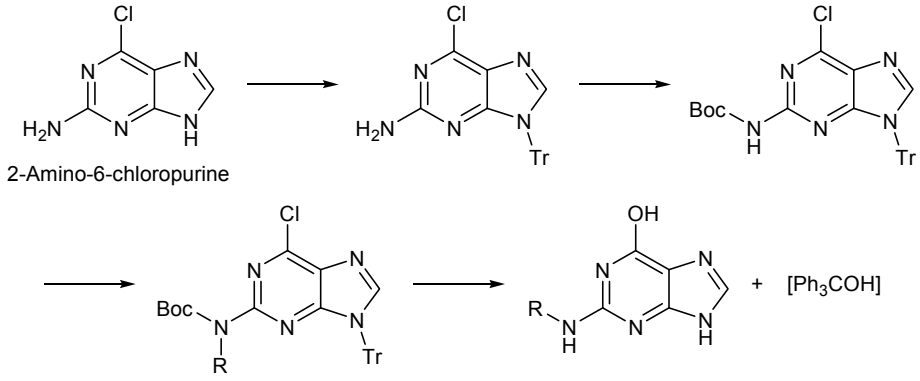
DOI: 10.1134/S1070428019060198

Guanine is one of the four main nucleobases found in the nucleic acids DNA and RNA playing the key role in living cells [1]. Many guanine derivatives have been used as anticancer and antiviral agents for decades [2–7]. Among numerous guanine derivatives, some N^2-substituted guanines exhibit interesting biological activities such as thymidine kinase inhibitory activity, antimicrobial activity, and cyclin-dependent kinase inhibitory activity [8–11]. In addition, some N^2-substituted guanines serve as synthetic intermediates for the preparation of nucleobase-containing drugs, molecular biological tools, diagnostic agents, etc. [12, 13]. Thus, facile and efficient synthetic protocols would be of great benefit.

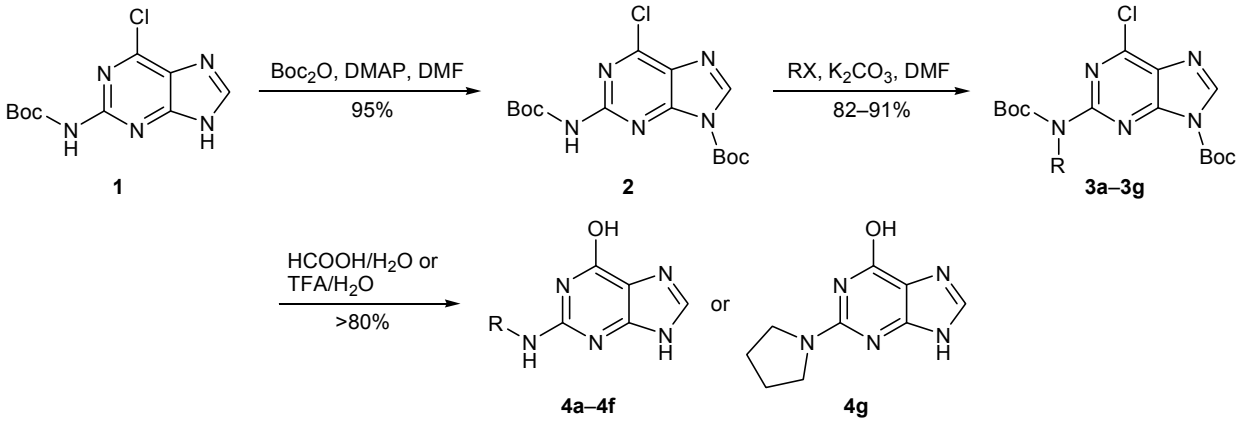
So far, several synthetic approaches have been reported for the synthesis of N^2-substituted guanines. The most frequently used method is the reaction of 2-halopurines with primary amines at elevated temperatures [14]. However, many 2-halopurines are costly and not easily available. Other approaches include the reductive amination of 2-aminopurines with aldehydes and classical N-alkylation of the corresponding amide followed by diacylation [15, 16]. Recently, Fletcher and coworkers reported a concise access to a series of N^2-alkylated guanines from 2-amino-6-chloropurine (Scheme 1) [17]. The key strategy involved trityl protection at the N^9 position and the Mitsunobu reaction at the exocylic 2-amino group. However, we feel that the trityl protection is not good enough, since triphenylmethanol is produced as by-product, which has to be removed by silica gel flash column chromatography. Due to the poor solubility and the high polarity of these guanines, this work-up process is not welcomed.

To develop a more efficient and practical synthetic protocol, we improved Fletcher's method. Herein, we

Scheme 1.



Scheme 2.



3, **4**, R = Me (**a**), Et (**b**), Bu (**c**), CH_2=$CHCH_2$ (**d**), MeC≡CCH_2 (**e**), $PhCH_2$ (**f**); **3g**, R = $Br(CH_2)_4$.

report the detailed investigations about the synthesis of these N^2-alkylated guanines.

Our synthesis of **4** is shown in Scheme 2. Purine **1** protected at the 2-amino group was prepared in two steps from 2-amino-6-chloropurine and used as starting material [18]. Purine **1** was first subjected to Boc protection at N^9 position in near-quantitative yield, and compound **2** was treated with alkyl halides under basic conditions to afford a series of N^2-alkylated guanines. As shown in Table 1, purines **3a**–**3g** were synthesized in very good yields using a broad range of halides, including benzyl, allyl, butynyl, and other primary aliphatic halides. However, the reactions with secondary aliphatic halides failed to give the desired compound (Table 1, entry no. 8). Finally, the hydrolytic dechlorination and Boc removal were accomplished in very good yields in one pot by treatment with a mixture of acid/water for 2 h at 75°C to afford the target compounds. These N^2-alkylated guanines were purified by simple trituration in a mixture of petroleum ether and ethyl acetate. Thus, column chromatography was spared, making the purification process more convenient.

In conclusion, we have developed a convenient three-step synthetic approach to N^2-alkylated guanines **4a**–**4g** in good overall yields from easily available N^2-Boc purine **1**. This procedure has a potential for scale-up productions.

EXPERIMENTAL

Commercial reagents were used without further purification. The boiling range of petroleum ether is 60–90°C. Melting points were measured on a SGW X-4 (INESA) temperature apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer or a Bruker DRX-500 (500 MHz) spectrometer. ^{13}C NMR spectra were obtained on a JNM-EX400 (100 MHz) spectrometer. High resolution mass spectra (ESI) were determined on a Bruker MicroTof II mass spectrometer. Low resolution mass spectra (EI) were determined with an Agilent 5975C mass-selective detector. IR spectra were obtained using KBr disks on a Bruker Tensor 27 FTIR instrument.

***tert*-Butyl 2-[(*tert*-butoxycarbonyl)amino]-6-chloro-9*H*-purine-9-carboxylate (2)**. 4-Dimethylaminopyridine (0.23 g, 1.8 mmol), was added to a suspension of purine **1** (10.0 g, 37.1 mmol) and Boc_2O (8.1 g, 37.1 mmol) in DMF (50 mL). The mixture was stirred at room temperature for 1 h, the solvent was removed under reduced pressure, and the residuewas extracted with ethyl acetate (100 mL). The organic layer was washed with 1 M HCl (70 mL) and brine (70 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the crude product, which

Table 1. Alkylation of compound **2** at the 2-amino group

Entry no.	Alkylating agent	Product	Yield, %
1	Iodomethane	**3a**	91
2	Iodoethane	**3b**	90
3	1-Iodobutane	**3c**	85
4	Allyl bromide	**3d**	85
5	1-Bromobut-2-yne	**3e**	87
6	Benzyl bromide	**3f**	89
7	1,4-Dibromobutane	**3g**	82
8	2-Iodopropane	–	No reaction

was triturated with a 5:1 mixture of petroleum ether and ethyl acetate. Yield 13.0 g (95%), white solid, mp 126–127°C. IR spectrum, ν, cm^{-1}: 3221, 2984, 1744, 1138. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.40 s (1H, H_{arom}), 7.76 s (1H, NH), 1.72 s [9H, $C(CH_3)_3$], 1.54 s [9H, $C(CH_3)_3$]. ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 154.0, 152.4, 152.1, 149.8, 145.6, 142.5, 128.4, 87.8, 81.9, 28.2, 27.9. Found: *m*/*z* 392.1106 $[M + Na]^+$. $C_{15}H_{20}ClN_5NaO_4$. Calculated: *M* + Na 392.1102.

General procedure for the synthesis of 3a–3g. All substitution reactions were run on the same scale, using the following general procedure.

***tert*-Butyl 2-[(*tert*-butoxycarbonyl)(methyl)amino]-6-chloro-9*H*-purine-9-carboxylate (3a).** Methyl iodide (0.58 g, 4.1 mmol) was added to a mixture of purine **2** (1.00 g, 2.7 mmol) and potassium carbonate (0.75 g, 5.4 mmol) in DMF (4 mL). The mixture was stirred at room temperature until the reaction was complete and extracted with ethyl acetate (2×15 mL). The extract was washed with water (2× 12 mL), dried over Na_2SO_4, and concentrated in vacuo to give brown oil, which was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 5:1). Yield 0.98 g (91%), pale solid, mp 107–109°C. IR spectrum, ν, cm^{-1}: 2984, 1712, 1364, 1137, 1014. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.46 s (1H, H_{arom}), 3.49 s (3H, CH_3), 1.70 s [9H, $C(CH_3)_3$], 1.54 s [9H, $C(CH_3)_3$]. ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 157.1, 153.5, 151.4, 151.2, 145.9, 143.0, 128.5, 87.3, 82.0, 35.3, 28.1, 27.9. Found: *m*/*z* 406.1269 $[M + Na]^+$. $C_{16}H_{22}ClN_5NaO_4$. Calculated: *M* + Na 406.1258.

***tert*-Butyl 2-[(*tert*-butoxycarbonyl)(ethyl)amino]-6-chloro-9*H*-purine-9-carboxylate (3b).** The product was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 8:1). Yield 0.97 g (90%), white solid, mp 68.6–71°C. IR spectrum, ν, cm^{-1}: 2990, 1743, 1570, 1154. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.46 s (1H, H_{arom}), 4.05 q (2H, CH_2, *J* = 7.0 Hz), 1.70 s [9H, $C(CH_3)_3$], 1.54 s [9H, $C(CH_3)_3$], 1.29 t (3H, CH_3, *J* = 7.0 Hz). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 156.7, 153.2, 151.4, 151.2, 146.0, 143.0, 128.5, 87.3, 81.8, 43.3, 28.1, 28.0, 14.0. Found: *m*/*z* 420.1417 $[M + Na]^+$. $C_{17}H_{24}ClN_5NaO_4$. Calculated: *M* + Na 420.1415.

***tert*-Butyl 2-[(*tert*-butoxycarbonyl)(butyl)amino]-6-chloro-9*H*-purine-9-carboxylate (3c).** The product was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 8:1). Yield 0.98 g (85%), white solid, mp 53–55°C. IR spectrum, ν, cm^{-1}: 2957, 1760, 1559, 1357, 1129. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.39 s (1H, H_{arom}), 3.88–3.94 m (2H, CH_2N), 1.58–1.66 m [11H, CH_2, $C(CH_3)_3$], 1.46 s [9H, $C(CH_3)_3$], 1.25–1.30 m (2H, CH_2), 0.85 t (3H, CH_3, *J* = 7.4 Hz). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 156.9, 153.5, 151.4, 151.2, 146.0, 143.1, 128.6, 87.3, 81.7, 77.2, 48.0, 30.9, 28.1, 27.9, 20.1, 13.8. Found: *m*/*z* 448.1731 $[M + Na]^+$. $C_{19}H_{28}ClN_5NaO_4$. Calculated: *M* + Na 448.1728.

***tert*-Butyl 2-[(*tert*-butoxycarbonyl)(prop-2-en-1-yl)amino]-6-chloro-9*H*-purine-9-carboxylate (3d).** The product was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 5:1). Yield 0.94 g (85%), yellow solid, mp 90–92°C. IR spectrum, ν, cm^{-1}: 2993, 1740, 1612, 1129. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.33 s (1H, H_{arom}), 5.80–5.89 m (1H, CH), 5.12 d.d (1H, CH_2, *J* = 17.2, 1.3 Hz), 4.99 d.d (1H, CH_2, *J* = 10.3, 1.1 Hz), 4.48 d (2H, CH_2N, *J* = 5.5 Hz), 1.57 s [9H, $C(CH_3)_3$], 1.40 s [9H, $C(CH_3)_3$]. ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 156.5, 153.1, 151.4, 151.2, 146.0, 143.1, 133.7, 128.7, 116.83, 87.3, 82.1, 50.3, 28.1, 28.0. Found: *m*/*z* 432.1404 $[M + Na]^+$. $C_{18}H_{24}ClN_5NaO_4$. Calculated: *M* + Na 432.1415.

***tert*-Butyl 2-[(*tert*-butoxycarbonyl)(but-2-yn-1-yl)amino]-6-chloro-9*H*-purine-9-carboxylate (3e).** The product was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 5:1). Yield 0.99 g (87%), white solid, mp 68.5–70.4°C. IR spectrum, ν, cm^{-1}: 3109, 2990, 1710, 1241, 1152. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.51 s (1H, H_{arom}), 4.77 d (2H, CH_2N, *J* = 2.2 Hz), 1.78 t (3H, *J* = 2.1 Hz), 1.75 s [9H, $C(CH_3)_3$], 1.58 s [9H, $C(CH_3)_3$]. ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 155.9, 152.6, 151.3, 146.0, 143.1, 128.8, 87.4, 82.5, 78.5, 77.3, 74.9, 38.0, 28.1, 27.9, 3.6. Found: *m*/*z* 444.1434 $[M + Na]^+$. $C_{19}H_{24}ClN_5NaO_4$. Calculated: *M* + Na 444.1415.

***tert*-Butyl 2-[benzyl(*tert*-butoxycarbonyl)amino]-6-chloro-9*H*-purine-9-carboxylate (3f).** The product was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 5:1). Yield 1.1 g (89%), white solid, mp 104–105°C. IR spectrum, ν, cm^{-1}: 3094, 2981, 1748, 1146, 945. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.84 s (1H, H_{arom}), 7.23–7.36 m (5H, H_{arom}), 5.11 s (2H, CH_2N), 1.56 s [9H, $C(CH_3)_3$], 1.40 s [9H, $C(CH_3)_3$]. ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 156.7, 153.3, 151.4, 151.3, 146.0, 143.1, 138.3, 128.7, 128.2, 127.5, 127.1,

87.3, 82.2, 51.2, 28.0, 27.9. Found: *m*/*z* 482.1585 $[M + Na]^+$. $C_{22}H_{26}ClN_5NaO_4$. Calculated: *M* + Na 482.1571.

***tert*-Butyl 2-[(4-bromobutyl)(*tert*-butoxycarbonyl)amino]-6-chloro-9*H*-purine-9-carboxylate (3g).** The product was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 10:1). Yield 1.12 g (82%), white solid, mp 76.4–78.7°C. IR spectrum, ν, cm^{-1}: 3115, 2984, 1753, 1700, 1147. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 8.40 s (1H, H_{arom}), 3.97 t (2H, CH_2N, *J* = 7.0 Hz), 3.38 t (2H, CH_2Br, *J* = 6.6 Hz), 1.83–1.88 m (2H, CH_2), 1.74–1.81 m (2H, CH_2), 1.64 s [9H, $C(CH_3)_3$], 1.47 s [9H, $C(CH_3)_3$]. ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 156.6, 153.5, 151.5, 151.3, 145.8, 143.2, 128.7, 87.4, 82.1, 47.0, 33.3, 30.0, 28.1, 28.0, 27.4. Found: *m*/*z* 526.0847/528.0828 $[M + Na]^+$. $C_{19}H_{27}BrClNaN_5O_4$. Calculated: *M* + Na 526.0833/528.0812.

General procedure for the synthesis of 4a–4g. The hydrolytic dechlorination and Boc removal for all compounds **4a**–**4g** were run on the same scale, using the following general procedure.

2-(Methylamino)-9*H*-purin-6-ol (4a). Purine **3a** (1 g, 2.6 mmol) was added to a 4:1 mixture of formic acid and water, and the mixture was stirred at 75°C overnight and evaporated to dryness to give the crude product, which was triturated with MeOH (2 mL). Yield 0.36 g (85%), yellow solid, mp > 300°C. IR spectrum, ν, cm^{-1}: 3302, 2661, 1700, 1613. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 11.87 s (1H, OH), 9.07 s (1H, H_{arom}), 7.50 s (1H, NH), 2.84 s (3H, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 155.4, 153.7, 150.5, 136.7, 108.0, 28.1. Found: *m*/*z* 166.0725 $[M + H]^+$. $C_6H_7N_5O$. Calculated: *M* + H 166.0651.

2-(Ethylamino)-9*H*-purin-6-ol (4b). The crude product was triturated with acetone (2 mL). Yield 0.40 g (86%), white solid, mp 246–247°C. IR spectrum, ν, cm^{-1}: 3350, 2720, 1700, 1612, 1463. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 11.53 s (1H, OH), 8.79 s (1H, H_{arom}), 7.39 s (1H, NH), 3.30 d.d (2H, CH_2, *J* = 7.1, 5.4 Hz), 1.14 t (3H, CH_3, *J* = 7.2 Hz). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 154.3, 151.2, 136.7, 109.3, 35.9, 14.8. Found: *m*/*z* 180.0883 $[M + H]^+$. $C_7H_9N_5O$. Calculated: *M* + H 180.0885.

2-(Butylamino)-9*H*-purin-6-ol (4c). The crude product was triturated with acetone (2 mL). Yield 0.45 g (83%), white solid, mp 287–288°C [8]. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm:11.69 s (1H, OH), 8.95 s (1H, H_{arom}), 7.65 s (1H, NH), 3.27 d.d (2H, CH_2, *J* = 12.4, 6.7 Hz), 1.46–1.55 m (2H, CH_2), 1.30–1.39 m (2H, CH_2), 0.89 t (3H, CH_3, *J* = 7.3 Hz). Found: *m*/*z* 208.1177 $[M + H]^+$. $C_9H_{13}N_5O$. Calculated: *M* + H 208.1198.

2-(Prop-2-en-1-ylamino)-9*H*-purin-6-ol (4d). The crude product was triturated with acetone (2 mL). Yield 0.43 g (87%), white solid, mp 230–231°C. IR spectrum, ν, cm^{-1}: 3265, 2737, 1683, 1603. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 11.82 s (1H, OH), 8.93 s (1H, H_{arom}), 7.70 s (1H, NH), 5.87–5.95 m (1H, CH), 5.25 d (1H, CH_2, *J* = 17.3 Hz), 5.13 d (1H, CH_2, *J* = 10.4 Hz), 3.94 s (2H, CH_2N). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 154.6, 154.0, 150.8, 136.7, 134.8, 116.1, 108.9, 43.1. Found: *m*/*z* 192.0878 $[M + H]^+$. $C_8H_9N_5O$. Calculated: *M* + H 192.0885.

2-(But-2-yn-1-ylamino)-9*H*-purin-6-ol (4e). The product was prepared according to the general procedure, but trifluoroacetic acid was used in place of formic acid. The crude product was triturated with MeOH (2 mL). Yield 0.46 g (87%), gray solid decomposing at 272°C. IR spectrum, ν, cm^{-1}: 3212, 3052, 2616, 1602, 1469. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 12.69 s (1H, OH), 10.59 (1H, H_{arom}), 7.74 s (1H, NH), 6.48 s (1H), 4.02 s (2H, CH_2), 1.78 s (3H, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 156.5, 152.1, 137.6, 100.0, 79.7, 78.7, 77.0, 30.9, 3.5. Found: *m*/*z*: 204.0883 $[M + H]^+$. $C_9H_9N_5O$. Calculated: *M* + H 204.0885.

2-(Benzylamino)-9*H*-purin-6-ol (4f). The crude product was triturated with acetone (2 mL). Yield 0.50 g (80%), yellow solid, mp 230–231°C; published data [8]: mp 225–228°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 12.06 br.s (1H, OH), 9.17 s (1H, H_{arom}), 8.23 s (1H, NH), 7.44 d (5H, H_{arom}, *J* = 41.0 Hz), 4.68 s (2H, CH_2). Found: *m*/*z* 242.1042 $[M + H]^+$. $C_{12}H_{11}N_5O$. Calculated: *M* + H 242.1042.

2-(Pyrrolidin-1-yl)-9*H*-purin-6-ol (4g). The crude product was triturated with acetone (2 mL). Yield 0.43 g (81%), white solid decomposing at 251°C. IR spectrum, ν, cm^{-1}: 3371, 2737, 1692, 1138. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 11.43 s (1H, OH), 9.11 s (1H, H_{arom}), 3.47–3.49 m (4H, CH_2), 1.93 br.s (4H, CH_2). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 154.6, 152.4, 150.5, 137.1, 107.1, 47.9, 25.2. Found: *m*/*z* 206.1027 $[M + H]^+$. $C_9H_{11}N_5O$. Calculated: *M* + H 206.1042.

ACKNOWLEDGMENTS

The authors thank the Laboratory of Organic Functional Molecules, the Sino–French Institute of ECNU, for supports.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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