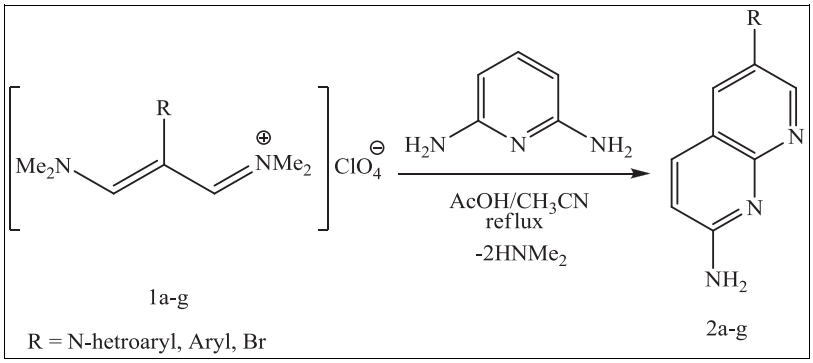
A Novel Synthesis of New 1,8-Naphthyridine Derivatives Using the Reaction of Vinamidinium Salts With 2,6-Diaminopyridine

Enayatollah Bahman Jahromi and Abdolmohammad Mehranpour*

Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr 75169, Iran
*E-mail: ammehranpour@hotmail.com

Additional Supporting Information may be found in the online version of this article.
Received February 7, 2016
DOI 10.1002/jhet.2694
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



Some new substituted 1,8- naphthyridines 2a–g have been synthesized by treating various 2-substituted vinamidinium salts 1a–g with 2,6-diaminopyridine. The structures of the synthesized compounds have been established on the basis of elemental analysis and spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR, UV/VIS, and mass).

INTRODUCTION

Among the different kind of heterocycles which have been investigated for the growing pharmaceutically significant molecules, 1,8-naphthyridines have had an important part in medicinal chemistry. Because the 1,8-naphthyridine skeleton exists in many compounds being separated from natural substances with different biological functions. Some of these 1,8-naphthyridine derivatives have fascinated chemists to a large extent. It was said that 1,8-naphthyridines had antibacterial, [1,2] antimycobacterial [3], antitumor [4], anti-inflammatory [5], antiplatelet [6], gastric antisecretory [7], antiallergic [8], local anesthetic [9] and benzodiazepine receptor activity [10]. It was also reported that these 1,8-naphthyridines were associated with positive ionotropic [11], β-adrenergic blocking [12], and antihypertensive activities [13]. In recent years, the design and synthesis of naphthyridines as a strong and particular antiviral inhibitor have been expressed [14,15].

The main synthetic processes that are utilized to produce different sorts of 1,8-naphthyridine system include condensation of 2-aminopyridine derivatives with carbonyl compounds which contain an activated methylene group [16–22] or with β-ketoesters [23]. The other common method to prepare 1,8-naphthyridine is condensation of ethanolic 2-amino-3-formylpyridines, in the presence of piperidine base, with active methylene compounds, aldehydes, acylic, and cyclic ketones [24,25].

It has been proved that the Vilsmeier-Haack reagent is a multipurpose reagent which is capable of performing many synthetic transformations [26]. It is applied in formylation [27], cyclohaloaddition [28], cyclization [29] and ring annulations [30]. We have synthesized the novel 1,8-naphthyridine derivatives using the reaction of 2-substituted vinamidinium salts with 2,6-diaminopyridine. It is noteworthy that although many derivatives of 1,8-naphthyridines have been synthesized [16–25,31,32], to the best of our knowledge, up to date there is no report on the synthesis of these derivatives using 2-substituted vinamidinium salts as starting compounds. The structure of the compounds were confirmed on the basis of their spectral (^{1}H-NMR, ^{13}C-NMR, IR, UV/VIS, and Mass) data and elemental analysis.

RESULTS AND DISCUSSION

A facile and efficient procedure for the preparation of the functionalized 1,8-naphthyridine derivatives by reaction of 2-substituted vinamidinium salts and 2,6-diaminopyridine catalyzed by acetic acid is described. This new protocol has the advantages of good yields and convenient operation. The most used method of preparation, exemplified in Table 2, starts from a 2-substituted vinamidinium salt which is converted into a 1,8-naphthyridine by means of reaction with

2,6-diaminopyridine. 2-Substituted vinamidinium salts were synthesized by means of Vilsmeier-Arnold formylation [30,33]. In this study, several conditions were tested at first, including diverse solvents, temperatures, and catalysts in order to find the best reaction conditions for the synthesis of **2a–g**. The effects of solvents and catalysts were evaluated for this reaction, and the results are summarized in Table 1. The reactions were carried out from 2–substituted vinamidinium salt **1a** (R = 4-tert-butylpyridine) and 2,6-diaminopyridine as a model reaction (Table 2). When ethanol was used as the solvent and the mixture was subjected to reflux, the desired product, **2a**, was obtained in low yields (25%, 35%, entries 2, and 3) after 12 h. In a modified protocol, the reaction was performed in acetonitrile as the solvent, obtaining significant improvements evidenced by better yields of the target product (75%), and shorter reaction times. As it is clearly observed in entries one and eight, the reaction did not take place without a catalyst. So, we performed the reaction with acidic catalyst. Results showed that both the aluminum chloride and the zinc chloride in conventional refluxing favored the product of **2a** (Table 1), but the yields were not very high, whereas acetic acid favored the formation of product in higher yields in acetonitrile as solvent. The best catalyst, acetic acid, was therefore chosen as the catalyst for this new transformation. To determine the extent of application of the cyclization reaction, the same conditions were used for some selected 2-substituted vinamidinium salts to get the 1,8-naphthyridine derivatives **2a–g** (Table 2).

A possible mechanism for the formation of 1,8-naphthyridine derivatives **2a–g** is shown in Scheme 1. It seems that the reaction proceeds via the initial attack of amino group to vinamidinium salt and then elimination of dimethylamine occurs in presence of acetic acid as catalyst. Finally, an intramolecular nucleophilic cyclization occurs on the iminium salt to produce the product. All 1,8-naphthyridine derivatives **2a–g** are new compounds, the molecular structures of which were confirmed on the basis

Table 1

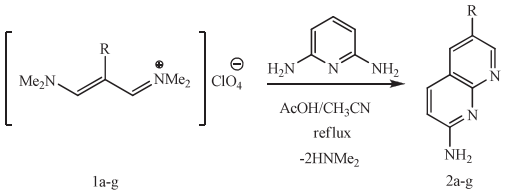
Optimization of reaction conditions for the synthesis of compound **2a**.

Catalyst	Conditions	Time (h)	Yield (%)[a]
–	EtOH, reflux	12	–
$AlCl_3$	EtOH, reflux	12	25
$ZnCl_2$	EtOH, reflux	12	35
AcOH	EtOH, reflux	12	40
AcOH	MeCN, reflux	3	75
$AlCl_3$	MeCN, reflux	12	45
$ZnCl_2$	MeCN, reflux	12	42
–	MeCN, reflux	12	–

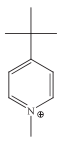
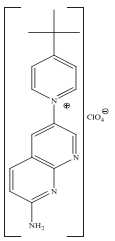
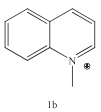
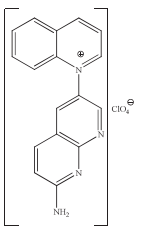
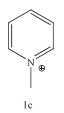
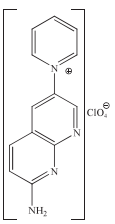
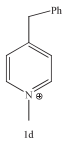
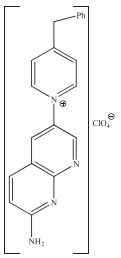
[a]Isolated yield.

Table 2

Synthesis of 1,8-naphthyridine derivatives **2a–g**.



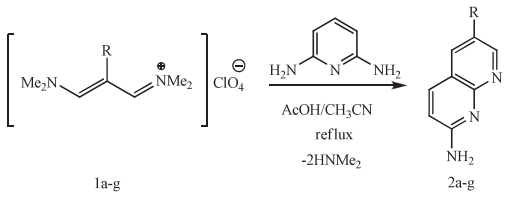
1a-g 2a-g

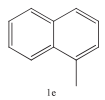
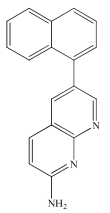
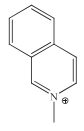
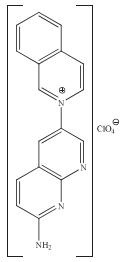
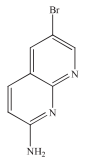
Entry	R	Product	Yield (%)[a]
1			75
	1a	2a	
2			68
	1b	2b	
3			72
	1c	2c	
4			70
	1d	2d	

(*Continued*)

Table 2

(Continued)



Entry	R	Product	Yield (%)[a]
5			65
6			58
7	Br 1g	 2g	62

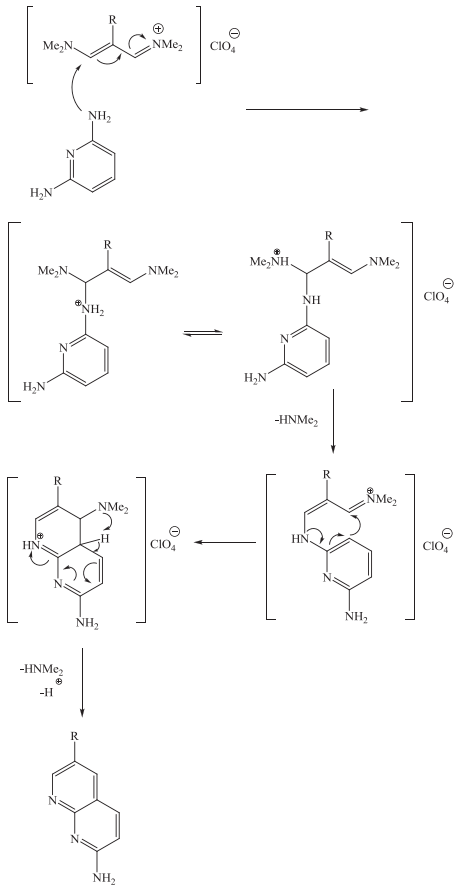
2 g

[a]Isolated yield.

of their spectral (^{1}H-NMR, ^{13}C-NMR, IR, UV/VIS, and mass) data.

In conclusion, seven novel substituted 1,8-naphthyridine derivatives were synthesized by reactions of 2-substituted vinamidinium salts with 2,6-diaminopyridine in good yields. The presented synthetic procedure is a simple and good yielding method for the preparation of compounds **2a–g**. The structures of all the new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, MS (mass spectrometry) spectra, and elemental analyses. The chemical shifts and multiplicities protons were in accordance with the expected values.

Scheme 1. Suggested reaction mechanism for the formation of 1,8-naphthyridine derivatives **2a–g**.



EXPERIMENTAL

Typical procedure for the synthesis of 2-(7-amino-1,8-naphthyridin-3-yl)isoquinolinium perchlorate (2f) as a derivative of 1,8-naphthyridines. 2-(1-(Dimethylamino)-3-(dimethylimino)prop-1-en-2-yl)isoquinolinium as 2-substituted vinamidinium salt was prepared according to procedures described by means of Vilsmeier-Arnold formylation [30,31]. To a vigorously stirring solution of 2-substituted vinamidinium salt (1.0 mmol, 0.454 g) and AcOH (1 mL) in CH_3CN (7.0 mL), was added dropwise a solution of 2,6-diaminopyridine (1.0 mmol, 0.109 g) in CH_3CN (3.0 mmol) under reflux. The mixture was allowed to reflux and stirred for 3 h after the addition was complete. When cooled to room temperature, the mixture was diluted with distilled H_2O (20 mL). The resulting precipitate was collected by filtration, washed with Et_2O (2×10 mL), and dried under vacuum at 80°C.

1-(7-Amino-1,8-naphthyridin-3-yl)-4-tert-butylpyridinium perchlorate [2a]. Chocolate powder; yield 75%; mp > 400°C; IR (KBr), (cm^{-1}): 3414, 2964, 1630, 1108; δ_H (400 MHz, d_6-DMSO) 1.46 (9H, s, CH_3), 7.20 (1 H, d, *J* 8.8 Hz), 7.50 (2 H, s, NH_2), 7.82 (1 H, d, *J* 8.8 Hz), 8.35

(2 H, d, *J* 6.8 Hz), 8.58 (1 H, d, *J* 2.4 Hz), 8.97 (1 H, d, *J* 2.4 Hz), 9.32 (2 H, d, *J* 6.8 Hz); δ_C (100 MHz, d_6-DMSO) 30.0, 37.1, 99.3, 104.8, 125.1, 125.5, 126.2, 144.6, 147.2, 147.9, 157.3, 159.3, 172.3; UV: λ_{max} (DMSO)/nm = 363; EI-MS (70ev): m/z = 279 [M^+]; *Anal*. Calcd for ($C_{17}H_{19}N_4$)(ClO_4): C, 53.89; H, 5.01; N, 14.73. Found: C, 53.11; H, 4.87; N, 14.12.

1-(7-Amino-1,8-naphthyridin-3-yl)quinolinium perchlorate [2b]. Dark brown powder; yield 68%; mp > 400°C; IR (KBr), (cm^{-1}): 3356, 3204, 1599, 1096; δ_H (400 MHz, d_6-DMSO) 7.24 (1 H, d, *J* 2 Hz), 7.50 (2 H, s, NH_2),7.88 (1 H, d, *J* 8.8 Hz), 8.19 (1 H, t, *J* 7.6 Hz), 8.38 (1 H, t, *J* 7.6 Hz), 8.47 (1 H, d, *J* 8 Hz), 8.61 (1 H, d, *J* 8 Hz), 8.71 (1 H, d, *J* 2.4 Hz), 8.77 (1 H, d, *J* 6.8 Hz), 9.12 (1 H, d, *J* 2.4 Hz), 9.16 (1 H, d, *J* 6.8 Hz), 10.48 (1 H, d, *J* 8 Hz); δ_C (100 MHz, d6-DMSO) 121.1, 126.2, 127.8, 127.9, 130.3, 131.5, 132.0, 132.9, 135.4, 135.8, 137.4, 138.0, 138.4, 145.7, 150.5, 150.8, 153.0; UV: λ_{max} (DMSO)/nm = 307; EI-MS (70ev): m/z = 273 [M^+]; *Anal*. Calcd for ($C_{17}H_{13}N_4$)(ClO_4): C, 54.78; H, 3.48; N, 15.02. Found: C, 53.49; H, 3.24; N, 15.60.

1-(7-Amino-1,8-naphthyridin-3-yl)pyridinium perchlorate [2c]. Orange powder; yield 72%; mp > 400°C; IR (KBr), (cm^{-1}): 3415, 3065, 1637, 1089; δ_H (400 MHz, d_6-DMSO) 7.19 (1 H, d, *J* 8.8 Hz), 7.77 (2 H, s, NH_2), 7.82 (1 H, d, *J* 8.8 Hz), 8.34 (2 H, t, *J* 7.2 Hz), 8.61 (1 H, d, *J* 1.8 Hz), 8.81 (1 H, t, *J* 8 Hz), 8.98 (1 H, d, *J* 2.8 Hz), 9.42 (2 H, dd, J_1 6.8 Hz, J_2 1.2 Hz); δ_C (100 MHz, d_6-DMSO) 105.7, 119.1, 121.1, 128.6, 130.4, 131.9, 132.7, 145.1, 145.3, 146.6, 150.7, 152.8; UV: λ_{max} (DMSO)/nm = 366; EI-MS(70ev): m/z = 222 [M^+]; *Anal*. Calcd for ($C_{14}H_{12}N_3$)(ClO_4): C, 52.26; H, 3.73; N, 13.05. Found: C, 51.94; H, 3.25; N, 14.20.

1-(7-Amino-1,8-naphthyridin-3-yl)-4-benzylpyridinium perchlorate [2d]. Dark brown powder; yield 70%; mp > 400°C; IR (KBr), (cm^{-1}): 3363, 3187, 2923, 1641, 1094; δ_H (400 MHz, d_6-DMSO) 4.41 (2 H, s, CH_2), 7.03 (1 H, d, *J* 9.1 Hz), 7.26–7.56 (5 H, m), 7.70 (2 H, s, NH_2), 8.05–8.17 (2 H, m), 8.20 (1 H, d, *J* 9.1 Hz), 8.43 (1 H, d, *J* 1.8 Hz), 8.49 (1 H, d, *J* 1.8 Hz), 8.96 (2 H, d, *J* 6.8 Hz); δ_C (100 MHz, d6-DMSO) 50.0, 117.3, 117.5, 117.8, 118.4, 118.5, 120.1, 120.8, 122.1, 122.4, 122.6, 124.9, 126.0, 146.2, 147.9, 155.0; UV: λ_{max} (DMSO)/nm = 440; EI-MS (70ev): m/z = 313 [M^+]; *Anal*. Calcd for ($C_{20}H_{17}N_4$)(ClO_4): C, 58.18; H, 4.11; N, 13.56. Found: C, 57.85; H, 4.46; N, 13.92.

6-Naphthalen-1-yl-1,8-naphthyridin-2-amine [2e]. Olivaceous powder; yield 65%; mp = 270°C; IR (KBr), (cm^{-1}): 3385, 3052, 1588, 1109; δ_H (400 MHz, d_6-DMSO) 7.48 (1 H, d, *J* 9.1 Hz), 7.69 (2 H, s, NH_2), 7.49–7.69 (7 H, m), 7.80 (1 H, d, *J* 9.1 Hz), 7.98 (1 H, d, *J* 2.1 Hz), 8.06 (1 H, d, *J* 2.1 Hz); δ_C (100 MHz, d_6-DMSO) 102.3, 124.8, 124.9, 125.0, 125.8, 126.1, 127.2, 128.1, 129.1, 129.9, 130.3, 130.9, 133.2, 134.1, 140.1, 140.2, 141.1, 164.3; UV: λ_{max} (DMSO)/nm = 315; EI-MS (70ev): m/z = 271 [M^+]; *Anal*. Calcd for ($C_{18}H_{13}N_3$): C, 79.68; H, 4.79; N, 15.48. Found: C, 79.02; H, 4.37; N, 14.98.

2-(7-Amino-1,8-naphthyridin-3-yl)isoquinolinium perchlorate [2f]. Brown powder; yield 58%; mp > 400°C; IR (KBr), (cm^{-1}): 3451, 3355, 1630, 1086; δ_H (400 MHz, d_6−DMSO) 7.03 (1 H, d, *J* 9.1 Hz), 7.39 (2 H, s, NH_2), 8.14–8.20 (2 H, m), 8.37 (1 H, t, *J* 8 Hz), 8.47 (1 H, d, *J* 8 Hz), 8.61 (1 H, d, *J* 6.3 Hz), 8.72 (1 H, d, *J* 1.8 Hz), 8.78 (1 H, d, *J* 7.7 Hz), 9.14 (1 H, d, *J* 6.3 Hz), 9.19 (1 H, d, *J* 1.8 Hz), 10.46 (1 H, s); δ_C (100 MHz, d_6-DMSO) 115.9, 116.0, 126.2, 127.81, 127.84, 131.5, 132.0, 132.9, 133.4, 135.5, 137.5, 138.1, 138.5, 147.5, 150.7, 157.7, 162.6; UV: λ_{max} (DMSO)/nm = 369; EI-MS (70ev): m/z = 273 [M^+]; *Anal*. Calcd for ($C_{17}H_{13}N_4$)(ClO_4): C, 54.78; H, 3.48; N, 15.02. Found: C, 54.11; H, 3.27; N, 15.60.

6-Bromo-1,8-naphthyridin-2-amine [2 g]. Dark orange powder; yield 62%; mp = 210°C; IR (KBr), (cm^{-1}): 3336, 3193, 1624, 1094; δ_H (400 MHz, d_6-DMSO) 7.11 (d, *J* 8.8 Hz, 1 H), 7.57 (s, 2 H, NH_2), 7.86 (d, *J* 8.8 Hz, 1 H), 8.59 (d, *J* 4.4 Hz, 1 H), 9.03 (d, *J* 4.4 Hz, 1 H); δ_C (100 MHz, d_6-DMSO) 115.2, 116.4, 136.4, 139.3, 140.3, 152.4, 159.6, 161.2; UV: λ_{max} (DMSO)/nm = 361; EI-MS (70ev): m/z = 224 [M]; *Anal*. Calcd for ($C_{18}H_6BrN_3$): C, 42.88; H, 2.70; N, 18.75. Found: C, 43.01; H, 2.92; N, 18.81.

Acknowledgments. Financial support of this work by the Research Council of the Persian Gulf University is gratefully acknowledged.

REFERENCES AND NOTES

[1] Bouzard, D.; DiCesare, P.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Remuzon, P.; Kessler, R. E.; Fung Tome, J. J Med Chem 1992, 35, 518.

[2] Rao, G. R.; Mogilaiah, K.; Sreenivasulu, B. Indian J Chem 1996, 35B, 339.

[3] Ferrarini, P. L.; Manera, C.; Mori, C.; Badawneh, M.; Saccomanni, G. Farmaco 1998, 53, 741.

[4] Zhang, S. X.; Bastow, K. F.; Tachibana, Y.; Kuo, S. C.; Hamel, E.; Mauger, A.; Narayanan, V. L.; Lee, K. H. J Med Chem 1999, 42, 4081.

[5] Kuroda, T.; Suzuki, F.; Tamura, T.; Ohmori, K.; Hosoe, H. J Med Chem 1992, 35, 1130.

[6] Ferrarini, P. L.; Badawneh, M.; Franconi, F.; Manera, C.; Miceli, M.; Mori, C.; Saccomanni, G. Farmaco 2001, 56, 311.

[7] Santilli, A.; Scotese, A. C.; Bauer, R. F.; Bell, S. C. J Med Chem 1987, 30, 2270.

[8] Kuo, S. C.; Tsai, S. Y.; Li, H. T.; Wu, C. H.; Ishii, K.; Nakamura, H. Chem Pharm Bull 1988, 36, 4403.

[9] Ferrarini, P. L.; Mori, C.; Tellini, N. Farmaco 1990, 45, 385.

[10] DaSettimo, A.; Primofiore, G.; DaSettimo, F.; Simorini, F.; Barili, P. L.; Senatore, G.; Martini, C.; Lucacchini, A. Drug Des Discov 1994, 11, 307.

[11] Herzig, S.; Heber, D.; Mescheder, A.; Reifenstein-Herzig, U.; Thormann, T.; Verborg, M.; Mohr, K. Arzneim Forsch 1994, 44, 937.

[12] Ferrarini, P. L.; Mori, C.; Badawneh, M.; Calderone, V.; Greco, R.; Manera, C.; Martinelli, A.; Nieri, P.; Saccomauni, G. Eur J Med Chem 2000, 35, 815.

[13] Ferrarini, P. L.; Mori, C.; Primofiore, G. J Heterocyclic Chem 1986, 23, 601.
[14] Chan, L.; Jin, H.; Stefanac, T.; Lavellee, J. F.; Falardeau, G.; Wang, W.; Bedard, J.; May, S.; Yuen, L. J Med Chem 1999, 42, 3023.
[15] Falardeau, G.; Chau, L.; Stefanac, T.; May, S.; Jin, H.; Lavalee, J. F. Bioorg Med Chem Lett 2000, 11, 2769.
[16] Chen, K.; Kuo, S. C.; Hsieh, M. C.; Mauger, A.; Lin, C. M.; Hamel, E.; Lee, K. H. J Med Chem 1997, 40, 2266.
[17] Chen, K.; Kuo, S. C.; Hsieh, M. C.; Mauger, A.; Lin, C. M.; Hamel, E.; Lee, K. H. J Med Chem 1997, 40, 3049.
[18] Mohamed, E. A.; Abdel-Rahman, R. M.; El-Gendy, Z.; Ismail, M. M. J Med Chem 1997, 40, 3049.
[19] Mohamed, E. A.; Abdel-Rahman, R. M.; El-Gendy, Z.; Ismail, M. M. J Indian Chem Soc 1994, 71, 765.
[20] Santilli, A. A.; Scotese, A. C.; Bauer, R. F.; Bell, S. C. J Med Chem 1987, 30, 2270.
[21] Seada, M.; El-Behairy, M. A.; Jahine, H.; Hanafy, F. Orient J Chem 1989, 5, 273.
[22] Nyce, P. L.; Steinman, M. Synthesis 1991, 571.
[23] Ferrarini, P. L.; Mori, C.; Primofiore, G.; Gazlolari, L. J Heterocyclic Chem 1990, 27, 881.
[24] Litvinov, V. P. Russ Chem Rev 2004, 73, 637.
[25] Rama, R. G.; Mogilaiah, K.; Sreenivasulu, B. Collect Czech Chem Commum 1989, 54, 1716.
[26] Bartuman, W.; Konz, E.; Ruger, W. Synthesis 1988, 9, 680.
[27] Vilsmeier, A.; Haack, A. Chem Ber 1927, 60, 119.
[28] Fujisawa, T.; Lida, S.; Sato, T. Chem Lett 1984, 1173.
[29] Venugopal, M.; Perumal, P. T.; Rajadurai, S. Tetrahedron Lett 1974, 15, 913.
[30] Kral, V.; Kanishchev, M. I.; Semenov, V. V.; Arnold, Z.; Shevelev, S. A.; Fainzilberg, A. A. Collect Czech Chem Commum 1988, 53, 1519.
[31] Reichardt, C.; Scheibelein, W. Tetrahedron Lett 1977, 18, 2087.
[32] Ge, H.; Liu, Q. Heterocycles 2015, 91, 1001.
[33] Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W. J Org Chem 1990, 55, 4735.