HETEROCYCLES, Vol. 96, No. 11, 2018, pp. 1889 - 1895. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 19th September, 2018, Accepted, 1st November, 2018, Published online, 19th November, 2018
DOI: 10.3987/COM-18-13988

NEW FACILE SYNTHESIS OF 3-SUBSTITUTED 7,8-DIHYDROQUINOLIN-5(6*H*)-ONES AND [1]BENZOPYRANO-[4,3-*b*]PYRIDIN-5-ONES USING 2-(HETERO)ARYLVINAMIDINIUM SALTS

Yiyi Weng,[a] Chen Sun,[a] Qingwei Cao,[a] Hantao Chen,[a] Nanhui Li,[a] Zhuo Chen,[a] and Weike Su[b]*

[a]College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China. [b]Collaborative Innovation Center of Yangtze River Delta Region Green of Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: pharmlab@zjut.edu.cn Fax: +86 (571)88871087

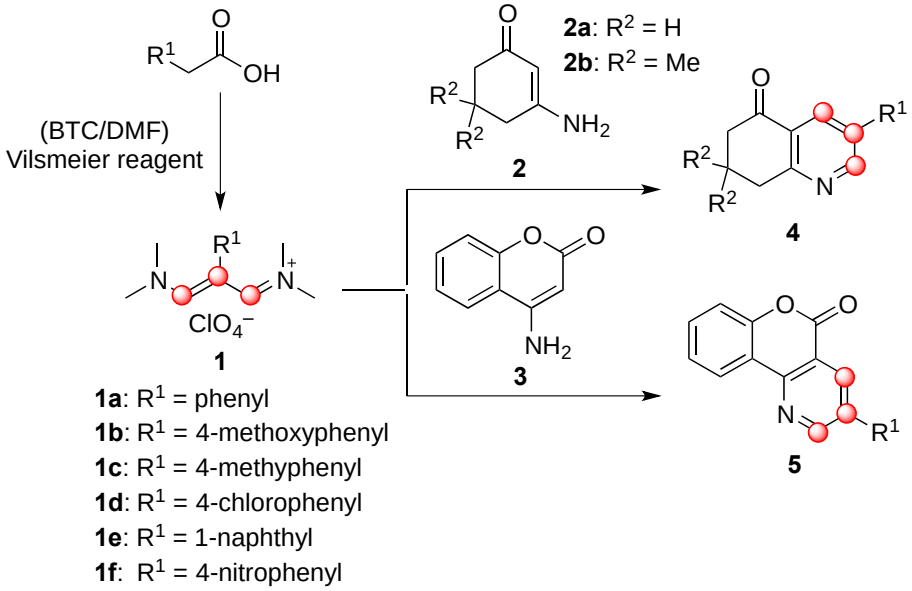
Abstract – The method of cyclocondensation of 3-amino-2-cyclohexen-1-ones **2** or 4-aminocoumarin **3** with symmetrical 2-(hetero)arylvinamidinium salts **1** has been developed, providing an efficient synthetic pathway to access novel functionalized 3-substituted 7,8-dihydroquinolin-5(6*H*)-ones **4** or [1]benzopyrano[4,3-*b*]pyridin-5-ones **5** in good to excellent yields. All the aryl-substituted and heterocyclic-substituted vinamidinium salts undergo a facile electrocyclic ring closure to form pyridine ring with α,β-unsaturated ketones. A possible mechanism for the formation of pyridine ring is proposed.

7,8-Dihydroquinolin-5(6*H*)-ones **4** and [1]benzopyrano[4,3-*b*]pyridin-5-ones **5** have attracted many attentions because of their potentially useful biological activities. 7,8-Dihydroquinolin-5(6*H*)-ones **4** have been reported to possess antitubercular[1] and antifungal[2] activities. [1]Benzopyrano[4,3-*b*]pyridin-5-ones (chromenopyridinone) **5** with 2*H*-chromen-2-one ring fused to a pyridine ring also exhibit a wide range of biological properties such as antimicrobial,[3,4] and anticancer.[5]

An inspection of the literatures showed that 7,8-dihydroquinolin-5(6*H*)-ones **4** were usually prepared via the reaction of propiolaldehyde with 3-amino-2-cyclohexen-1-ones **2**.[6] Three-components condensation of 1,3-cyclohexanedions, β-enaminones or α,β-unsaturated aldehydes, and ammonium acetate in the presence of $K_5CoW_{12}O_{40}·3H_2O$,[7] $CeCl_3·7H_2O$-NaI[8] or 4 Å molecular sieves[9] to produce

7,8-dihydroquinolin-5(6*H*)-ones **4** was also widely described. In addition, four-components of 1,3-cyclohexanedions, α,β-unsaturated aldehydes, 2-furylmethylamine and alcohols in the presence of Ce(IV) ammonium nitrate[10] can also synthesize 7,8-dihydroquinolin-5(6*H*)-ones **4**. [1]Benzopyrano-[4,3-*b*]pyridin-5-ones **5** can be synthesized via the reaction of salicylaldehydes with ethyl aminocrotonate,[11] condensation of 4-hydroxycoumarins[12] with α,β-unsaturated ketones under Kroehnke's conditions, and intramolecular cyclization reaction of 4-methyl-2-(methoxyphenyl)nicotinic acid[13] using Eaton's reagent (P_2O_5-$MeSO_3H$). However, a survey of these literatures reveals that most of methods suffered from low yields, harsh conditions, or difficult starting materials. In view of these facts, it is nesessary to develop an efficient route for synthesis of 7,8-dihydroquinolin-5(6*H*)-ones **4** and [1]benzopyrano[4,3-*b*]pyridin-5-ones **5** in a minimum number of steps from commercially available starting materials.

Vinamidinium salts **1**[14,15] have been utilized as the potential three-carbon building blocks in organic synthesis. It can undergo condensation reactions with bifunctional nucleophiles to form heterocycles such as pyrroles,[16] thiophenes,[17] pyrazoles,[18] pyrimidines,[19] pyridine[20] and pyridinone.[21] In this paper, we continued to explore the synthetic utility of vinamidinium salts reacted with bifunctional hetero-nucleophiles containing amino group and α,β-unsaturated ketone preparing 3-substituted 7,8-dihydroquinolin-5(6*H*)-ones **4** and [1]benzopyrano[4,3-*b*]pyridin-5-ones **5** (Scheme 1).



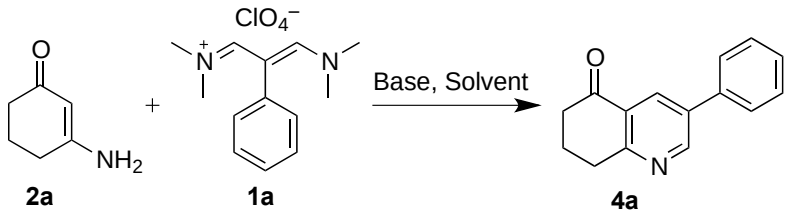
Scheme 1. Preparation of 3-substituted 7,8-dihydroquinolin-5(6*H*)-ones **4** and [1]benzopyrano[4,3-*b*]pyridin-5-ones **5**

The 2-(hetero)arylvinamidinium salts **1** were synthesized in good yields by reacting (hetero)arylacetic acids with Vilsmeier reagent (triphosgene/DMF) in DMF at 80 °C followed by quenching in aqueous

$NaClO_4$. In our method, Vilsmeier reagent $POCl_3$/DMF was replaced by eco-friendly triphosgene/DMF in order to avoid the formation of inorganic phosphoric acid salts. The 3-amino-2-cyclohexen-1-ones[22] **2** was easily prepared from readily available 1,3-cyclohexanediones and ammonium acetate. 4-Aminocoumarin[23] **3** could also be synthesized by 4-hydroxycoumarin with ammonium acetate.

We initiated our studies with 3-amino-2-cyclohexen-1-one **2a** and 2-arylvinamidinium salt **1a** as the model substrate (Table 1). From the results indicated in Table 1, strong bases such as KOBu^t or NaH resulted better yield (72%, 83%; Table 1, entries 1, 3), while a little weaker base like NaOMe made the yield drop sharply (24%; Table 1, entry 2). Increasing the reaction temperature afforded the lower yields (Table 1, entries 4, 5). With further optimization of solvents, DMF was chosen as the best solvent comparing with other solvent like acetonitrile and DCE (Table 1, entries 3, 7, 8). Subsequently, a series of expriments were performed to determine the appropriate ratio of the reagents (Table 1, entries 9-12). The best results were obtained when reaction of **2a** with 1.2 equiv. of **1a** was performed in DMF containing 3.0 equiv. of NaH at 10 °C for 0.5 h in 83% yield (Table 1, entry 3).

Table 1. Optimization of Reaction Conditions



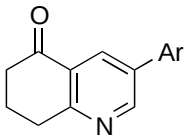
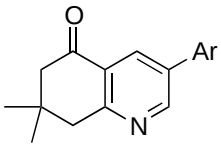
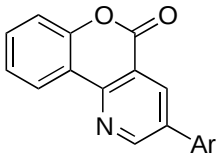
2a **1a** **4a**

Entry	Base	Solvent	Temp (°C)	**2a** : base	**2a** : **1a**	Yield (%)[a]
1	KOBu^t	DMF	10	1:3	1:1.2	72
2	NaOMe	DMF	10	1:3	1:1.2	24
3	NaH	DMF	10	1:3	1:1.2	83
4	NaH	DMF	25	1:3	1:1.2	70
5	NaH	DMF	80	1:3	1:1.2	30
6	NaH	DMF	0	1:3	1:1.2	62
7	NaH	MeCN	10	1:3	1:1.2	50
8	NaH	DCE	10	1:3	1:1.2	55
9	NaH	DMF	10	1:2	1:1.2	74
10	NaH	DMF	10	1:3	1:1.0	80
11	NaH	DMF	10	1:3	1:1.5	82
12	NaH	DMF	10	1:4	1:1.2	75

[a]Isolated yields after silica gel chromatography.

With the optimal reaction conditions in hand, the scope and generality of the reaction were investigated. Using the above optimal conditions, the reactions of various 2-arylvinamidinium salts **1b-f** with 3-amino-2-cyclohexen-1-one **2a** were studied. The results listed in Table 2 (entries 1-6), each of with the substrates behaved in a similar manner, affording the corresponding 3-substituted 7,8-dihydroquinolin-5(6*H*)-ones in good yields (65-85%; Table 2, entries 1-6).

Table 2. Synthesis of 3-substituted 7,8-dihydroquinolin-5(6*H*)-ones and [1]benzopyrano[4,3-*b*]-pyridin-5-ones from 2-arylvinamidinium salts

Entry	Substrates	Products	Ar	Yield(%)[d]
1	**1a**		C_6H_4- (**4a**)	83
2	**1b**		4-MeO-C_6H_4- (**4b**)	84
3	**1c**		4-Me-C_6H_4- (**4c**)	85
4	**1d**		4-Cl-C_6H_4- (**4d**)	75
5	**1e**	(**4a-4f**)[a]	1-naphthyl (**4e**)	65
6	**1f**		4-NO_2-C_6H_4- (**4f**)	77
7	**1a**		C_6H_4- (**4g**)	90 (81)[e]
8	**1b**		4-MeO-C_6H_4- (**4h**)	93
9	**1c**		4-Me-C_6H_4- (**4i**)	96
10	**1d**		4-Cl-C_6H_4- (**4j**)	83
11	**1e**	(**4g-4l**)[b]	1-naphthyl (**4k**)	75
12	**1f**		4-NO_2-C_6H_4-(**4l**)	87
13	**1a**		C_6H_4- (**5a**)	86 (80)[e]
14	**1b**		4-MeO-C_6H_4- (**5b**)	89
15	**1c**		4-Me-C_6H_4- (**5c**)	93
16	**1d**		4-Cl-C_6H_4- (**5d**)	74
17	**1e**	(**5a-5e**)[c]	1-naphthyl (**5e**)	76

[a]Conditions: a mixture of **1** (1.2 mmol), **2a (**1.0 mmol), NaH (3.0 mmol) in anhydrous DMF (10 mL) at 10 °C for 0.5 h.
[b]The reaction was carried out at 10 °C in DMF for 2 h using NaOMe (3.0 equiv.) as the base.
[c]The reaction was carried out at 80 °C in DMF for 3 h using NaOMe (3.0 equiv.) as the base.
[d]Isolated yields after silica gel chromatography.
[e]The yields in brackets were carried out in DMF using NaH (3.0 equiv.) as the base.

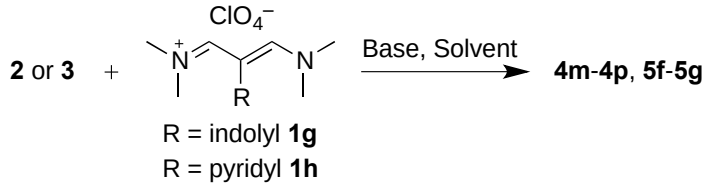
With optimized condition in hand, 3-amino-5,5-dimethylcyclohex-2-en-1-one **2b** could also be used to react with 2-arylvinamidinium salts **1a-1f** in this condition, but using NaOMe to replace NaH could get better yields in our experiments (75-96%; Table 2, entries 7-12). As the results showed in Table 2 (entries

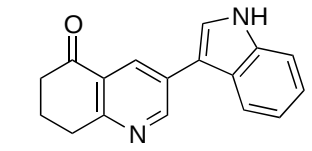
1-12), employing 3-amino-5,5-dimethylcyclohex-2-en-1-one **2b** as substrate could get higher yields than 3-amino-2-cyclohexen-1-one **2a**. The 2-arylvinamidinium salts **1** bearing the relative electron-donating groups at the *para*-position gave higher yields than those bearing electron-withdrawing groups. The 2-naphthyl appended vinamidinium salt **1e** gave relatively lower yields due to the steric hindrance effect (Table 2, entries 5, 11).

It would be specially mentioned that 4-aminocoumarin **3** was proven to be a suitable substrate to react with 2-arylvinamidinium salts **1a**-**1e** in DMF using NaOMe as base. The expected products 3-substituted [1]benzopyrano[4,3-*b*]pyridin-5-ones **5a**-**5e** were observed in moderate good yields (74-93%; Table 2, entries 13-17). It should be pointed out that the reaction needed to be conducted at higher temperature (80 °C).

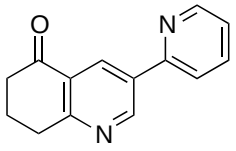
During our studies to further expand the scope of this methodology, 2-indolyl appended vinamidinium salt **1g** and 2-pyridyl appended vinamidinium salt **1h** were also investigated (Table 3). The substrates **4**

Table 3. Synthesis of 3-substituted 7,8-dihydroquinolin-5(6*H*)-ones and [1]benzopyrano[4,3-*b*]-pyridin-5-ones from 2-heteroarylvinamidinium salts

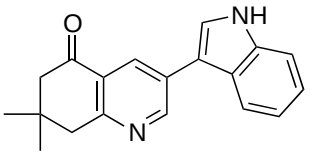




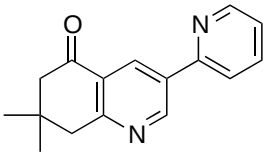
4m[a] 75%



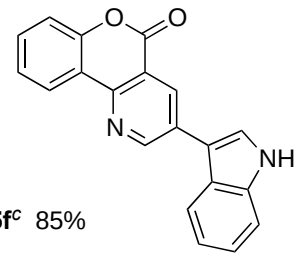
4n[a] 71%



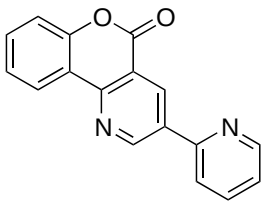
4o[b] 90%



4p[b] 87%



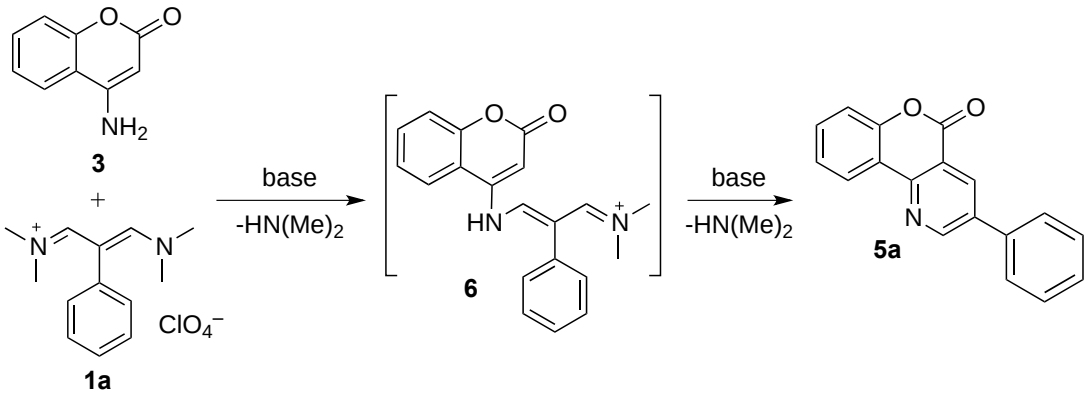
5f[c] 85%



5g[c] 77%

[a]The reaction was carried out at 25 °C in DMF for 1 h using NaH (3.0 equiv.) as the base.
[b]The reaction was carried out at 80 °C in DMF for 2 h using NaOMe (3.0 equiv.) as the base.
[c]The reaction was carried out at 80 °C in DMF for 3 h using NaOMe (3.0 equiv.) as the base.

and **5** underwent reactions smoothly to yield the targeted products **4m-4p**, **5f-5g** in moderate to good yields (71-90%; Table 3).



Scheme 2. Plausible reaction mechanism

We hypothesize that the amino group of aminocoumarin **3** attacks the electrophilic carbon of the vinamidinium salt **1a** to get the intermediate **6** after an elimination of dimethylamine.[24] Then, cyclization of the intermediate **6** followed by the loss of another dimethylamine affords the final product **5a** (**Scheme 2**).

In summary, a facile and efficient one-pot synthesis of novel 3-substituted 7,8-dihydroquinolin-5(6*H*)-ones **4** and [1]benzopyrano[4,3-*b*]pyridin-5-ones **5** was described in this paper. The advantages of this route were simple operation, mild reaction conditions, readily available starting materials and high yield of the products.

ACKNOWLEDGEMENTS

We thank the National Natural Science Foundation of China (NSFC) (Grant No. 21506190) and Natural Science Foundation of Zhejiang Province (No. LQ16B060005) for financial support.

SUPPORTING INFORMATION

Supplementary (synthesis of the starting azides, HPLC chromatograms, IR, 1H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26076/96/11.

REFERENCES

1. (a) S. Kantevari, S. R. Patpi, B. Sridhar, P. Yogeeswari, and D. Sriram, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1214; (b) B. Tanwar, A. Kumar, P. Yogeeswari, D. Sriram, and A. K. Chakraborti, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5960.

2. A. R. Gholap, K. S. Toti, F. Shirazi, R. Kumari, M. K. Bhat, M. V. Deshpande, and K. V. Srinivasan, *Bioorg. Med. Chem.*, 2007, **15**, 6705.
3. I. A. Khan, M. V. Kulkarni, M. Gopal, M. S. Shahabuddin, and C.-M. Sun, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3584.
4. F. A. El-Essawy and A.-A. S. El-Etrawy, *J. Heterocycl. Chem.*, 2014, **51**, 191.
5. (a) M. S. Al-Said, M. M. Ghorab, and Y. M. Nissan, *Chem. Cent. J.*, 2012, **6**, 64; (b) N. Mulakayala, D. Rambabu, M. R. Raja, M. Chaitanya, C. S. Kumar, A. M. Kalle, G. R. Krishna, C. M. Reddy, M. V. B. Rao, and M. Pal, *Bioorg. Med. Chem.*, 2012, **20**, 759.
6. (a) N. A. LeBel and B. W. Caprathe, *J. Org. Chem.*, 1985, **50**, 3938; (b) G. Chen, Z. Wang, X. Zhang, and X. Fan, *J. Org. Chem.*, 2017, **82**, 11230.
7. S. Kantevari, M. V. Chary, and S. V. N. Vuppalapati, *Tetrahedron*, 2007, **63**, 13024.
8. S. Kantevari, S. R. Patpi, D. Addla, S. R. Putapatri, B. Sridhar, P. Yogeeswari, and D. Sriram, *ACS Comb. Sci.*, 2011, **13**, 427.
9. F. Liéby-Muller, C. Allais, T. Constantieux, and J. Rodriguez, *Chem. Commun.*, 2008, 4207.
10. V. P. A. Raja, G. Tenti, S. Perumal, and J. C. Menéndez, *Chem. Commun.*, 2014, **50**, 12270.
11. P. A. Navarrete-Encina, R. Salazar, C. Vega-Retter, K. Pérez, J. A. Squella, and L. J. Nuñez-Vergara, *J. Braz. Chem. Soc.*, 2010, **21**, 413.
12. S. U. Pandya, U. R. Pandya, B. R. Hirani, and D. I. Brahmbhatt, *J. Heterocycl. Chem.*, 2006, **43**, 795.
13. Y. Tagawa, K. Yamagata, and K. Sumoto, *Lett. Org. Chem.*, 2006, **3**, 759.
14. Z. Arnold, *Coll. Czech. Chem. Commun.*, 1965, 2125.
15. I. W. Davies, J.-F. Marcoux, J. Wu, M. Palucki, E. G. Corley, M. A. Robbins, N. Tsou, R. G. Ball, P. Dormer, R. D. Larsen, and P. J. Reider, *J. Org. Chem.*, 2000, **65**, 4571.
16. J. Yang, G. Su, Y. Ren, and Y. Chen, *Tetrahedron*, 2014, **70**, 8642.
17. R. T. Clemens and S. Q. Smith, *Tetrahedron Lett.*, 2005, **46**, 1319.
18. Y. M. Poronik, G. Clermont, M. Blanchard-Desce, and D. T. Gryko, *J. Org. Chem.*, 2013, **78**, 11721.
19. O. V. Maltsev, A. Pöthig, and L. Hintermann, *Org. Lett.*, 2014, **16**, 1282.
20. S. Tian, Y. Mao, Y. Jiang, and G. Xu, *Synlett*, 2018, **29**, 949.
21. S. Q. Smith, S. T. Dudek, S.-H. He, J. A. Girod, and S. R. Nunes, *Tetrahedron Lett.*, 2013, **54**, 3965.
22. G.-W. Wang and C.-B. Miao, *Green Chem.*, 2006, **8**, 1080.
23. B. Stamboliyska, V. Janevska, B. Shivachev, R. P. Nikolova, G. Stojkovic, B. Mikhova, and E. Popovski, *ARKIVOC*, 2010, **x**, 62.
24. Y. Sawai, M. Mizuno, T. Ito, and M. Yamano, *Tetrahedron*, 2014, **70**, 2370.