HETEROCYCLES, Vol. 83, No. 2, 2011, pp. 365 - 370. © The Japan Institute of Heterocyclic Chemistry
Received, 5th November, 2010, Accepted, 16th December, 2010, Published online, 27th December, 2010
DOI: 10.3987/COM-10-12098

A FACILE SYNTHESIS OF 2-SUBSTITUTED 2,3-DIHYDRO-4(1*H*)-AZULENO[1,2-*d*]PYRIMIDINONES

Dao-Lin Wang,[a*] Yuan-Feng LI,[a] Jiao Xu,[b] Wei Li,[a] Shao-Fei Li,[a] and Li-Nan Lin[a]

[a] Liaoning Key Laboratory of Synthesis and Application of Functional Compound, College of Chemistry & Chemical Engineering, Bohai University, Jinzhou 121001, P. R. China

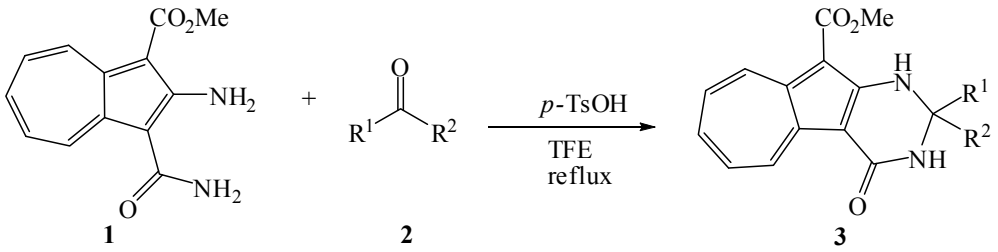
[b] Department of Cosmetolog, Jiamusi Institute, Heilongjiang University of Chinese Medicine, Jiamusi 154007, P. R. China

Abstract - A facile, efficient and novel approach to access 2-substituted 2,3-dihydro-4(1*H*)-azuleno[2,1-*d*]pyrimidinones was developed by condensation of methyl 2-amino-3-carbamoylazulene-1-carboxylate with ketones or ary1 aldehydes in the 2,2,2-trifluoroethanol catalyzed by *p*-toluenesulfonic acid.

A variety of heterocycle-fused azulenes have so far been obtained on the viewpoints of chemical properties and physiological activities by several synthetic methods.[1-4] In a previous paper, we reported that 1-acetyl-2-(bromomethyl)azulene reacted with anilines or thio-acetamide to give 2-aryl-3-methylazuleno[1,2-*c*]pyrroles[5] or azuleno[1,2-*c*]thiophenes[6] respectively. Of them, pyrimidine-fused azulenes were prepared by using different types of stating materials as followings. 2-Amino-1-formylazulene reacted with guanidine to convert to 2-aminoazuleno[2,1-*d*]pyrimidine.[7] When the reaction of 2-acetylimino-2*H*-cyclohepta[*b*]furan derivatives with active methylene compounds to afford the azuleno[2,1-*d*]pyrimidine derivatives.[8] Quite recently, we have reported the synthesis of 4-*N*-arylaminoazuleno[2,1-*d*]pyrimidines by the reactions of 1-cyano-2-*N*,*N*-dimethylformamidinylazulenes with anilines.[9]

On the other hand, 2,3-dihydro-4(1*H*)-quinazolinone derivatives are important bicyclic heterocycles due to their wide range of biological activities such as anticancer,[10] inhibitors of cell multiplication,[11] antispermatogenic agent,[12] diuretic,[13] and antibacterial activities.[14]

In connection with our studies on the synthetic utilities of heterocycle-fused azulenes, this paper describes with the preparation of 2-substituted 2,3-dihydro-4(1*H*)-azuleno[2,1-*d*]pyrimidinones (**3**) by the condensation of methyl 2-amino-3-carbamoylazulene-1-carboxylate (**1**) with ketones or ary1 aldehydes (**2**).



Scheme 1

Trifluoroethanol(TFE) have been proven to be advantageous to some kinds of organic reaction due to their distinguished physiochemical properties,[15] such as low nucleophilicity，high polarity and strong hydrogen bond donating ability.[16] In the present study, the favorable solvent effect of TFE in the cyclization reaction of methyl 2-amino-3-carbamoylazulene-1-carboxylate with ketones or ary1 aldehydes in the TFE catalyzed by *p*-toluenesulfonic acid was observed.

The typical procedure for the synthesis of 2-substituted 2,3-dihydro-4(1*H*)-azuleno [2,1-*d*]pyrimidinones was described as follows: Treatment of methyl 2-amino-3-carbamoylazulene-1-carboxylate (**1**) (1.0 equiv.) with ketones or aldehydes (**2**) (1.2 equiv.) in the presence of TsOH (0.1 equiv.) in refluxing TFE.

As methyl 2-amino-3-carbamoylazulene-1-carboxylate was subjected to benzaldehyde, a yield of 93% was obtained in TFE within 8 h. In comparison, when me same reaction was carried out in ethanol instead of TFE, the product was obtained only in 46% yield. As the reaction time was prolonged for 24 h, the desired product was obtained in 77% yield. Furthermore, the reaction of methyl 2-amino-3-carbamoylazulene-1-carboxylate with benzaldehyde did not proceed at all in the refluxing TFE in the absence of TsOH, implying TsOH as a catalyst in the reaction.

Therefore, on the basis of the above experimental results, it is suggested that TsOH is a catalyst for the cyclization reaction, however the high po1arity and hydrogen bonding interaction of TFE with reactants must have played some important roles in promoting the reaction of methyl 2-amino-3-carbamoylazulene-1-carboxylate (**1**) with ketone or aldehyde derivatives (**2**).

As shown in Table l, the reaction of methyl 2-amino-3-carbamoylazulene-1-carboxylate (**1**) with ketones or aromatic aldehydes (**2**) smoothly proceeded to give the corresponding 2-substituted 2,3-dihydro-4(1*H*)-azuleno[2,1-*d*]pyrimidinones (**3**) in good yields.

Table 1. Condensation of methyl 2-amino-3-carbamoylazulene-1-carboxylate (**1**) with ketones or aromatic aldehydes (**2a-j**)

Entry	Product （**3**）	**2**		Time /h	Yield /%
		R^1	R^2		
1	**3a**	H	C_6H_4	8	93
2	**3b**	H	4-MeC_6H_4	8	90
3	**3c**	H	4-$MeOC_6H_4$	9	88
4	**3d**	H	4-FC_6H_4	10	92
5	**3e**	Me	Me	6	87
6	**3f**	Me	Et	7	85
7	**3g**	Me	*i*-Pr	10	81
8	**3h**	Me	C_6H_4	48	24
9	**3i**	-$(CH_2)_4$-		6	93
10	**3j**	-$(CH_2)_5$-		7	90

As anticipated, due to the unfavourable electronic and steric effect, the reaction rate of the acetophenone was much slower than that of aromatic aldehydes, only 24% yield was obtained in 48 h (Table l, entry 8). The treatment of cyclic and acyclic alkyl ketones with **1** afforded the corresponding 2,3-dihydro-4(1*H*)-azuleno[2,1-*d*]pyrimidinones in excellent yields (81-93%) within 6-10 h (Table l, entries 5-7, 9, 10).

In conclusion, it was found that the reaction of methyl 2-amino-3-carbamoylazulene-1-carboxylate with ketones or aromatic aldehydes in the 2,2,2-trifluoroethanol catalyzed by *p*-toluenesulfonic acid, provided a facile and efficient method for synthesis of 2-substituted 2,3-dihydro-4(1*H*)-azuleno[2,1-*d*]-pyrimidinones in good yields.

EXPERIMENTAL

All melting points were determined with a Yanaco MP JP-3 apparatusand are uncorrected. The infrared (IR) spectra were measured on a JascoA-102 IR spectrophotometer. 1H NMR spectra were recorded on Bruker spectrometer (300MHz). Elemental analyzes were performed on EA 2400 Ⅱ elemental analyzer (Perkin-mlmer).

Preparation of 2-substituted 2,3-dihydro-4(1*H*)-azuleno[2,1-*d*]pyrimidin ones.

General procedure: To a solution of methyl 2-amino-3-carbamoylazulene-1- carboxylate[17] (**1**, 0.5 mmol) in trifluoroethanol (TFE) (15 mL) was added ketones or aromatic aldehydes (**2**, 0.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.05 mmol) and the reaction mixture was refluxed for the

appropriate time (see Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, was cooled and diluted with water (25 mL). The precipitate was collected, washed with water, dried, and purified by column chromatography on silica gel (160-200 mesh) using pertroleum ether-EtOAc (5:1) as eluent to afford the corresponding products. The physical and spectra data of the compounds **3a-j** are as follows:

2-Phenyl-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimidinone (3a): Pale yellow prisms (from EtOAc). mp 222-224 ºC; IR (KBr, cm^{-1}): *v* 3280(NH), 3226(NH), 1644(C=O), 1628 (C=O). ^{1}H-NMR ($CDCl_3$): δ 3.93 (3H, s, $COOCH_3$), 5.55 (1H, s, NH), 6.20 (1H, s, CH), 7.36 (1H, s, NH), 7.44-7.46 (3H, m), 7.52 (1H, dd, *J* = 9.6, 9.6 Hz), 7.57-7.62 (4H, m), 9.07 (1H, d, *J* = 10.0 Hz), 9.31 (1H, d, *J* = 10.0 Hz). *Anal*. Calcd for $C_{20}H_{16}N_2O_3$: C 72.28, H 4.85, N 8.43. Found C 72.31, H 4.77, N 8.24.

2-(4'-Methylphenyl)-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimidi none (3b): Pale yellow prisms (from EtOAc). mp 197-199 ºC; IR (KBr, cm^{-1}): *v* 3276(NH), 3219(NH), 1648(C=O), 1631(C=O). ^{1}H-NMR($CDCl_3$): *δ* 2.38 (3H, s, CH_3), 3.92 (3H, s, $COOCH_3$), 5.75 (1H, s, NH), 6.16 (1H, s, CH), 7.23 (2H, d, *J* = 7.6 Hz), 7.31 (1H, s, NH), 7.47 (2H, d, *J* = 7.6 Hz), 7.53 (1H, dd, *J* = 9.6, 9.6 Hz), 7.58-7.60 (2H, m), 9.06 (1H, d, *J* = 9.6 Hz), 9.30 (1H, d, *J* = 10.0 Hz). *Anal*. Calcd for $C_{21}H_{18}N_2O_3$: C 72.82, H 5.24, N 8.09. Found C 72.91, H 5.36, N 8.23.

2-(4'-Methoxyphenyl)-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimi dinone (3c): Pale yellow prisms (from EtOAc). mp 210-212 ºC; IR (KBr, cm^{-1}): *v* 3280(NH), 3225(NH), 1643(C=O), 1628(C=O). ^{1}H-NMR($CDCl_3$): δ 3.84 (3H, s, OCH_3), 3.93 (3H, s, $COOCH_3$), 5.51 (1H, s, NH), 6.16 (1H, s, CH), 6.95 (2H, d, *J* = 8.8 Hz), 7.28 (1H, s, NH), 7.52 (2H, d, *J* = 8.8 Hz), 7.54 (1H, dd, *J* = 9.6, 9.6 Hz), 7.58-7.62 (2H, m), 9.07 (1H, d, *J* = 9.6 Hz), 9.31 (1H, d, *J* = 9.6 Hz). *Anal*. Calcd for $C_{21}H_{18}N_2O_4$: C 69.60, H 5.01, N 7.73. Found C 69.73, H 5.17, N 7.89.

2-(4'-Fluorophenyl)-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimidi none (3d): Pale yellow prisms (from EtOAc). mp 251-253 ºC; (KBr, cm^{-1}): *v* 3278(NH), 3223(NH), 1644(C=O), 1635(C=O). ^{1}H-NMR($CDCl_3$): *δ* 3.94 (3H, s, $COOCH_3$), 5.72 (1H, s, NH), 6.21 (1H, s, CH), 7.14 (2H, d, *J* = 8.4 Hz), 7.35 (1H, s, NH), 7.52 (1H, dd, *J* = 9.6, 9.6 Hz), 7.61 (2H, d, *J* = 8.4 Hz), 7.70-7.72 (2H, m), 9.07 (1H, d, *J* = 10.0 Hz), 9.31 (1H, d, *J* = 10.0 Hz). *Anal*. Calcd for $C_{20}H_{15}FN_2O_3$: C 68.57, H 4.32, N 5.42. Found C 68.72, H 4.36, N 5.57.

2,2-Dimethyl-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimidinone (3e): Yellow needles (from benzene). mp 204-205 ºC; (KBr, cm^{-1}): *v* 3295(NH), 3153(NH), 1645(C=O), 1629(C=O). ^{1}H-NMR ($CDCl_3$): *δ* 1.66 (6H, s, 2xCH_3), 3.98 (3H, s, $COOCH_3$), 6.02 (s, 1H, NH), 7.29 (s, 1H, NH), 7.46 (1H, dd, *J* = 9.6, 9.6 Hz), 7.50 (1H, dd, *J* = 9.6, 9.6 Hz), 7.56 (1H, dd, *J* = 9.6, 9.6 Hz), 8.98 (1H, d, *J* = 10.0 Hz), 9.26 (1H, d, *J* = 10.0 Hz). *Anal*. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.42; H, 5.63; N, 9.84.

2-Ethyl-2-methyl-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimidinone (3f): Yellow needles (from benzene). mp 201-202 ºC; (KBr, cm^{-1}): *v* 3286(NH), 3175(NH), 1657(C=O), 1642(C=O). ^{1}H-NMR ($CDCl_3$): δ 1.05 (3H, t, *J* = 7.2 Hz, CH_3), 1.63 (3H, s, CH_3), 1.89 (2H, q, *J* = 7.2 Hz, CH_2), 3.98 (3H, s, $COOCH_3$), 5.51 (1H, s, NH), 7.29 (1H, s, NH), 7.46 (1H, dd, *J* = 9.2, 9.6 Hz), 7.50 (1H, dd, *J* = 9.6, 10.0 Hz), 7.53 (1H, dd, *J* = 9.6, 10.0 Hz), 8.96 (1H, d, *J* = 10.0 Hz), 9.23 (1H, d, *J* = 10.0 Hz). *Anal.* Calcd for $C_{17}H_{18}N_2O_3$: C 68.44, H 6.08, N 9.39. Found C 68.33, H 6.13, N 9.24.

2-Isopropyl-2-methyl-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimi dinone (3g): Yellow needles (from benzene). mp 194-196 ºC; (KBr, cm^{-1}): *v* 3296(NH), 3215(NH), 1659(C=O), 1632(C=O). ^{1}H-NMR($CDCl_3$): δ 0.99 (6H, d, 2xCH_3), 1.64 (3H, s, CH_3), 1.77 (2H, d, *J* = 6.0 Hz, CH_2), 1.98 (1H, m, CH), 3.98 (3H, s, $COOCH_3$), 5.36 (1H, s, NH), 7.31 (1H, s, NH), 7.45 (1H, dd, *J* = 9.6, 10.0 Hz), 7.50 (1H, dd, *J* = 9.2, 10.0 Hz), 7.55 (1H, dd, *J* = 9.2, 9.6 Hz), 8.96 (1H, d, *J* = 10.0 Hz), 9.24 (1H, d, *J* = 10.0 Hz). *Anal*. Calcd for $C_{18}H_{20}N_2O_3$: C 69.21, H 6.45, N 8.97. Found C 69.34, H 6.32, N 8.86.

2-Methyl-2-phenyl-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimidi none (3h): Pale yellow prisms (from benzene). mp 206-208 ºC; (KBr, cm^{-1}): *v* 3288(NH), 3224(NH), 1657(C=O), 1626(C=O). ^{1}H-NMR ($CDCl_3$): δ 2.01 (3H, s, CH_3), 3.98 (3H, s, $COOCH_3$), 6.08 (1H, s, NH), 7.28-7.30 (1H, m), 7.33-7.37 (2H, m), 7.50-7.54 (3H, m), 7.50 (1H,dd, *J* = 9.6, 9.6 Hz), 7.56-7.58 (2H, m), 7.78 (1H, s, NH), 9.02 (1H, d, *J* = 10.0 Hz), 9.24 (1H, d, *J* = 10.0 Hz). *Anal*. Calcd for $C_{21}H_{18}N_2O_3$: C 72.82, H 5.24, N 8.09. Found C 72.76, H 5.37, N 8.13.

2,2-Tetramethylene-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimidi none (3i): Yellow needles (from benzene). mp 192-193 ºC; (KBr, cm^{-1}): *v* 3265(NH), 3231(NH), 1663(C=O), 1631(C=O). ^{1}H-NMR($CDCl_3$): δ 1.84-1.88 (4H, m), 2.04-2.08 (4H, m), 3.96 (3H, s, $COOCH_3$), 6.02 (1H, s, brs), 7.42 (1H, s, NH), 7.46 (1H, dd, *J* = 9.2, 9.6 Hz), 7.51 (1H, dd, *J* = 9.6, 9.6 Hz), 7.53 (1H, dd, *J* = 9.6, 10.0 Hz), 8.95 (1H, d, *J* = 9.6Hz), 9.24 (1H, d, *J* = 10.0 Hz). *Anal*. Calcd for $C_{18}H_{18}N_2O_3$: C 69.66, H 5.85, N 9.03. Found C 69.75, H 5.73, N 9.14.

2,2-Pentamethylene-2,3-dihydro-10-methylcarbonyl-4(1*H*)-azuleno[2,1-*d*]pyrimidi none (3j): Yellow needles (from benzene). mp 226-227 ºC; (KBr, cm^{-1}): *v* 3282(NH), 3231(NH), 1654(C=O), 1631(C=O). ^{1}H-NMR($CDCl_3$): δ 1.43-1.48 (2H, m), 1.66-1.68 (4H, m), 1.86-1.90 (2H, m), 1.95-1.99 (2H, m), 3.96 (3H, s, $COOCH_3$), 6.15 (1H, s, NH), 7.29 (1H, s, NH), 7.44 (1H, dd, *J* = 9.6, 9.6 Hz), 7.49 (1H, dd, *J* = 9.6, 10.0 Hz), 7.51 (1H, dd, *J* = 9.6, 9.6 Hz), 7.62 (1H, s, NH), 8.96 (1H, d, *J* = 9.6 Hz), 9.22 (1H, d, *J* = 10.0 Hz). *Anal.* Calcd for $C_{19}H_{20}N_2O_3$: C 70.35, H 6.21, N 8.64. Found C 70.42, H 6.35, N 8.53.

We thank the Foundation of Innovation Team Project of Liaoning Education Department (No. 2008T001) for financial support.

REFERENCES

1. T. Morita, T. Nakadate, and K. Takase, *Heterocycles*, 1981, **15**, 835.
2. K. Fujimori, T. Fujita, K.Yamane, M. Yasunami, and K. Takase, *Chem. Lett*., 1983, **12**, 1721.
3. K. Yamane, K. Fujimori, S. Ichikawa, S. Miyoshi, and K. Hashizume, *Heterocycles*, 1983, **20**, 1263.
4. K. Fujimori, H. Fukazawa, Y. Nezu, K. Yasunami, and K. Takase, *Chem. Lett*., 1986, **15**, 1021.
5. D. L. Wang and K. Imafuku, *Heterocycles*, 2001, **54**, 647.
6. K. Imafuku and D. L. Wang, *Heterocycles*, 2002, **58**, 405.
7. T. Nozoe, T. Asao, and M. Kobayashi, *Bull. Chem. Soc. Jpn*., 1973, **46**, 3161.
8. K. Takase, T. Nakazawa, and T. Nozoe, *Heterocycles*, 1981, **15**, 839.
9. D. L. Wang, Z. Gu, J. Xu, S. Ha, and K. Imafuku, *Synth. Commun*., 2009, **39**, 2329.
10. a) M.-J. Hour, L. J. Huang, S. C. Kuo, Y. Xia, K. Bastow, Y. Nakanishi, E. Hamel, and K.-H. Lee, *J. Med. Chem*., 2000, **43**, 4479; b) G. M. Chinigo, M. Paige, S. Grindrod, E. Hamel, S. Dakshanamurthy, M. Chruszcz, W. Minor, and M. L. Brown, *J. Med. Chem*., 2008, **51**, 4620.
11. H. J. Yale and M. Kalkstein, *J. Med. Chem*., 1967, **10**, 334.
12. G. L. Neil, L. H. Li, H. H. Buskirk, and T. E. Moxley, *Cancer Chemother*., 1972, **56**, 163.
13. H. A. Parish, Jr., R. D. Gilliom, W. P. Purcell, R. K. Browne, R. F. Spirk, and H. D. White, *J. Med. Chem.*, 1982, **25***,* 98.
14. R. J. Alaimo and H. E. Russell, *J. Med. Chem.*, 1972, **15**, 335.
15. a) I. Ktement, H. Lütjens, and P. Knochel, *Angew. Chem., Int. Ed. Engl*., 1997, **36**, 1454; b) A. Ogawa and D. P. Curran, *J. Org. Chem*., 1997, **62**, 450.
16. a) M. J. Kamlet, J. L. M. Abboud, M. H. Abraham, and R. W. Taft, *J. Org. Chem*., 1983, **48**, 2877; b) J. P. Bégué, D. Bonnet-Delpon, and B. Crousse, *Synlett.*, 2004, **1**, 18.
17. T. Nozoe, K. Takase, T. Nakazawa, and S. Fukuda, *Tetrahedron*, 1971, **27**, 3357.