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

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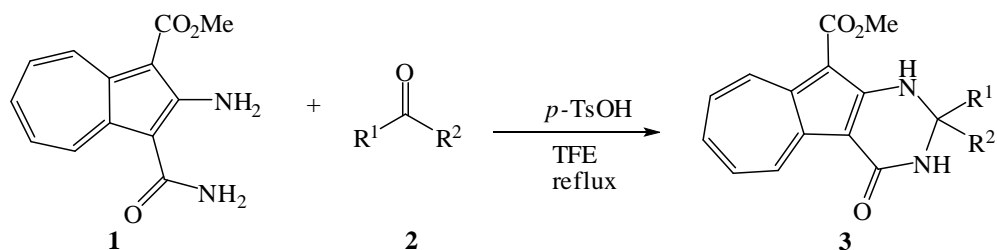
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Abstract - A facile, efficient and novel approach to access 2-substituted 2,3-dihydro-4(1*H*)-azuleno[2,1-*d*]pyrimidinones was developed by condensation of methyl 2-amino-3-carbamoylazulene-1-carboxylate with ketones or aryl aldehydes in the 2,2,2-trifluoroethanol 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*]pyrroles⁵ or azuleno[1,2-*c*]thiophenes⁶ respectively. Of them, pyrimidine-fused azulenes were prepared by using different types of starting 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-acetylmino-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 aryl aldehydes (**2**).



Scheme 1

Trifluoroethanol (TFE) has been proven to be advantageous to some kinds of organic reaction due to their distinguished physicochemical 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 aryl 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 the 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 polarity 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 1, 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 ₆ H ₄	8	93
2	3b	H	4-MeC ₆ H ₄	8	90
3	3c	H	4-MeOC ₆ H ₄	9	88
4	3d	H	4-FC ₆ H ₄	10	92
5	3e	Me	Me	6	87
6	3f	Me	Et	7	85
7	3g	Me	<i>i</i> -Pr	10	81
8	3h	Me	C ₆ H 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 1, 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 1, 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 apparatus and are uncorrected. The infrared (IR) spectra were measured on a Jasco A-102 IR spectrophotometer. ¹H NMR spectra were recorded on Bruker spectrometer (300 MHz). Elemental analyzes were performed on EA 2400 II elemental analyzer (Perkin-Elmer).

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-carboxylate¹⁷ (**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 petroleum 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(1H)-azuleno[2,1-d]pyrimidinone (3a): Pale yellow prisms (from EtOAc). mp 222-224 °C; IR (KBr, cm^{-1}): ν 3280(NH), 3226(NH), 1644(C=O), 1628 (C=O). $^1\text{H-NMR}$ (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 $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_3$: 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(1H)-azuleno[2,1-d]pyrimidinone (3b): Pale yellow prisms (from EtOAc). mp 197-199 °C; IR (KBr, cm^{-1}): ν 3276(NH), 3219(NH), 1648(C=O), 1631(C=O). $^1\text{H-NMR}$ (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 $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3$: 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(1H)-azuleno[2,1-d]pyrimidinone (3c): Pale yellow prisms (from EtOAc). mp 210-212 °C; IR (KBr, cm^{-1}): ν 3280(NH), 3225(NH), 1643(C=O), 1628(C=O). $^1\text{H-NMR}$ (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 $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4$: 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(1H)-azuleno[2,1-d]pyrimidinone (3d): Pale yellow prisms (from EtOAc). mp 251-253 °C; IR (KBr, cm^{-1}): ν 3278(NH), 3223(NH), 1644(C=O), 1635(C=O). $^1\text{H-NMR}$ (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 $\text{C}_{20}\text{H}_{15}\text{FN}_2\text{O}_3$: 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(1H)-azuleno[2,1-d]pyrimidinone (3e): Yellow needles (from benzene). mp 204-205 °C; IR (KBr, cm^{-1}): ν 3295(NH), 3153(NH), 1645(C=O), 1629(C=O). $^1\text{H-NMR}$ (CDCl_3): δ 1.66 (6H, s, $2\times\text{CH}_3$), 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 $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$: 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(1H)-azuleno[2,1-d]pyrimidinone (3f): Yellow needles (from benzene). mp 201-202 °C; (KBr, cm^{-1}): ν 3286(NH), 3175(NH), 1657(C=O), 1642(C=O). $^1\text{H-NMR}$ (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 $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3$: 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(1H)-azuleno[2,1-d]pyrimidinone (3g): Yellow needles (from benzene). mp 194-196 °C; (KBr, cm^{-1}): ν 3296(NH), 3215(NH), 1659(C=O), 1632(C=O). $^1\text{H-NMR}$ (CDCl_3): δ 0.99 (6H, d, $2 \times \text{CH}_3$), 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 $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_3$: 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(1H)-azuleno[2,1-d]pyrimidinone (3h): Pale yellow prisms (from benzene). mp 206-208 °C; (KBr, cm^{-1}): ν 3288(NH), 3224(NH), 1657(C=O), 1626(C=O). $^1\text{H-NMR}$ (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 $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3$: 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(1H)-azuleno[2,1-d]pyrimidinone (3i): Yellow needles (from benzene). mp 192-193 °C; (KBr, cm^{-1}): ν 3265(NH), 3231(NH), 1663(C=O), 1631(C=O). $^1\text{H-NMR}$ (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, $J = 9.6$ Hz), 9.24 (1H, d, $J = 10.0$ Hz). *Anal.* Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$: 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(1H)-azuleno[2,1-d]pyrimidinone (3j): Yellow needles (from benzene). mp 226-227 °C; (KBr, cm^{-1}): ν 3282(NH), 3231(NH), 1654(C=O), 1631(C=O). $^1\text{H-NMR}$ (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 $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3$: C 70.35, H 6.21, N 8.64. Found C 70.42, H 6.35, N 8.53.

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