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Photochemical and thermal cyclizations of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones for the synthesis of 4-methylenepyrimidino[5,4-*b*]indol-2-ones

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ABSTRACT

Photochemical and thermal cyclization of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones could afford fused indoles, such as 1,2,3a,9b-tetrahydro-4-methylenepyrimidino[5,4-*b*]indol-2-ones and 1,3,5,6,7a,12b-hexahydroquinazolino[9,4-*b*]indol-2,7-dione in high yields via nitrene electrophilic addition and rearrangement reactions.

The chemistry of organic azides has long attracted the attention of chemists since their discovery more than a century ago.[1] In particular, an increasing interest could be observed in the past two decades due to their vast synthetic utility in conjunction with their easy accessibility via various synthetic routes.[2] The photoreaction of organic azides are well known and are widely used in synthetic organic chemistry,[1–3] photolithography,[3a] and photoaffinity labeling of biopolymers.[4] It is commonly believed that photolysis of the organic azides could afford the very reactive singlet nitrenes after releasing of molecule nitrogen. The intermolecular insertion of nitrenes into C–H bonds or addition to double bonds generally lead to nitrogen-containing heterocycles. For example, photolysis of *o*-azidostyrenes afforded mainly indole derivatives via insertion of a phenylnitrene into the β-carbon–H bond of an adjacent double bond;[1,2,5] and photolysis of *o*-azidophenyl substituted crotonates produced aziridino[1,2-*a*]indoline via the addition of a phenylnitrene to double bonds.[6] Comparatively, no report was found for the investigation of photoreaction of 3-(*o*-azidophenyl)cycloalkene in the literatures. As a continuance of our studies on the photoreaction of aryl azides with double bonds,[7] we report herein a concise and efficient synthesis of fused indoles, such as 1,2,3a,9b-tetrahydro-4-methylenepyrimidino[5,4-*b*]indol-2-ones, 1,3,5,6,7a,12b-hexahydroquinazolino[9,4-*b*]indol-2,7-dione by the photochemical or thermal cyclization of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones (**1a–j**) as shown in Scheme 1.

Pyrimidino[5,4-*b*]indoles and quinazolino[9,4-*b*]indoles are well known for their potential biological and pharmacological activities,[8] such as analgesic, anti-allergy, bactericide, anti-infective, antihypertensive, anti-inflammatory, and antitumor activities and can be used as blood platelet aggregation inhibitors, gastric cancer inhibitors, HIV-1 RT inhibitors, ulcer inhibitors, virucidal and neoplasm inhibitors, and vasodilators. So several other methods have also been established for the synthesis of the similar fused aromatic compounds. For example, cyclocondensation of *N*-[3-(2-ethoxycarbonyl)indolyl]urea to give pyrimido[5,4-*b*]indolo-2,4-dione;[8a] cyclocondensation of *N*-[3-(2-ethoxycarbonyl)indolyl] amidines with amines to give pyrimido[5,4-*b*]indolo-2-one.[8b] Cyclocondensation of *N*-[3-(2-ethoxycarbonyl)indolyl]thiourea to give 2-thiopyrimido[5,4-*b*]indolo-2,4-dione.[8d]

Ten 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones (**1a–j**) were prepared from 2-azidobenzaldehyde, 1,3-dicarbonyls, and urea or 1,3-dimethylurea or thiourea by the Biginelli reactions.[9] We first investigated the reactions of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-one (**1a**) under different conditions (Table 1). The

Scheme 1. Photochemical and thermal cyclizations of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones **1a–j**.

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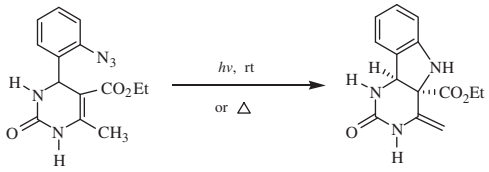
Table 1
Photochemical and thermal cyclizations of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-one (**1a**) under different conditions



1a **2a**

Entry	Solvents	Reaction conditions	*t* (h)	Convn[a] (%)	Yield[b] (%)
1	CH_3COCH_3	*hv*, rt	5	92	46
2	CH_2Cl_2	*hv*, rt	6	87	55
3	CH_3CN	*hv*, rt	5	92	46
4	DMSO	*hv*, rt	6	98	82
5	Xylene	Reflux	24	55	40
6	Xylene–DMSO (5:1, v/v)	Reflux	24	72	62
7	DMSO	160 °C	12	87	65
8	DMF	Reflux	8	98	78

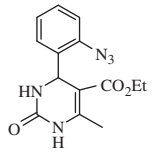
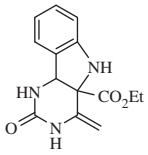
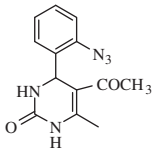
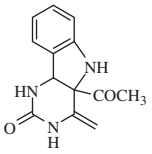
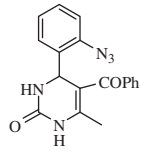
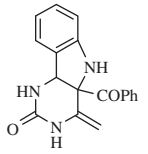
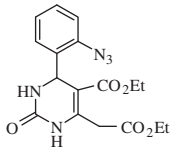
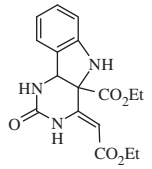
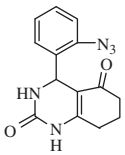
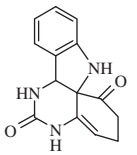
[a] Conversion was calculated on the basis of **1a**.
[b] Yield of isolated product based on consumed **1a**.

photoreactions of **1a** in different solvents, such as acetone, dichloromethane, and acetonitrile were examined, but the conversion of **1a** was much lower because **1a** was difficultly dissolved in these solvents. When DMSO was used as the solvent instead, it was found the conversion of **1a** was increased greatly under irradiation at λ >300 nm for certain time and **2a** was obtained as the sole product in high yield. Then, we examined the thermal reaction of **1a** under different conditions. When the thermal reaction was performed in refluxing xylene, the unsatisfactory result was obtained as listed in Table 1 probably because of the low solubility of **1a** in xylene and low temperature of refluxing xylene. The conversion and yield could be increased after the addition of DMSO to the xylene and long-time refluxing. Then the thermal reaction was tried in DMSO at 160 °C, an improved result was obtained. The best result was obtained from the thermolysis of **1a** in refluxing *N*,*N*-dimethylformaide (DMF). So the cyclization reactions of all other 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones were investigated under both irradiation in DMSO at room temperature and thermolysis in DMF under refluxing.

The photoreactions of other nine 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones (**1b–j**) were all conducted under selected reaction conditions for 5–6 h and the expected 1,2,3a,9b-tetrahydro-4-methylenepyrimidino[5,4-*b*]indol-3-ones or 1,3,5,6,7a,12b-hexahydroquinazolino[9,4-*b*]indol-2,7-dione (**2b–j**) were obtained as the major products in all cases (Table 2). All products were fully identified by ^{1}H NMR, ^{13}C NMR and MS,[10] and the structure of **2b** was further confirmed by the X-ray crystal analysis as depicted in Figure 1.[11] The thermal reactions of seven selected substrates were conducted in refluxing DMF, the same products as those obtained in photoreactions were obtained as major products and the results were also listed in Table 2. Obviously the photolytic process was a little more facile than the thermal process in yields of products.

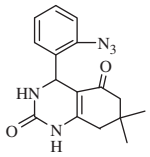
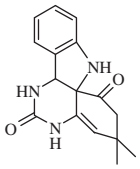
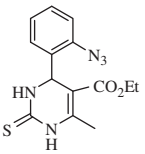
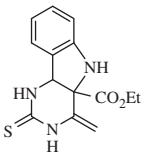
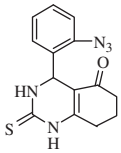
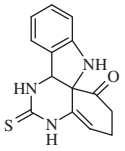
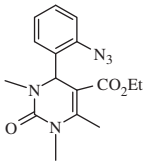
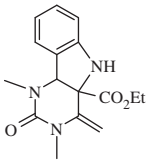
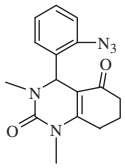
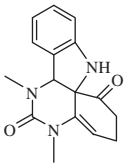
A mechanism is proposed for the transformation of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones (**1a**) into fused indoles 1,2,3a,9b-tetrahydro-4-methylenepyrimidino[5,4-*b*]indol-3-one (**2a**) under both photolytic and thermal reaction conditions as

Table 2
Photochemical and thermal cyclizations of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-one (**1a–j**)

Entry	Reactants		*t* (h)		Products		Yield (%)	
			hv[a]	Δ[b]			*hv*[a]	Δ[b]
1	**1a**		6	8	**2a**		82	78
2	**1b**		6	8	**2b**		78	75
3	**1c**		6	8	**2c**		80	81
4	**1d**		5	8	**2d**		85	72
5	**1e**		5	8	**2e**		85	80

(*continued on next page*)

Table 2 (*continued*)

Entry	Reactants	*t* (h)		Products	Yield (%)	
		hν[a]	Δ[b]		*hν*[a]	Δ[b]
6	**1f** 	5	–	**2f** 	75	–
7	**1g** 	6	–	**2g** 	76	–
8	**1h** 	6	8	**2h** 	80	74
9	**1i** 	6	–	**2i** 	85	–
10	**1j** 	5	8	**2j** 	86	84

[a] Photolysis was carried out under irradiation of 500 W medium pressure Hg lamp in DMSO at room temperatures.
[b] Thermolysis was carried out in DMF under refluxing.

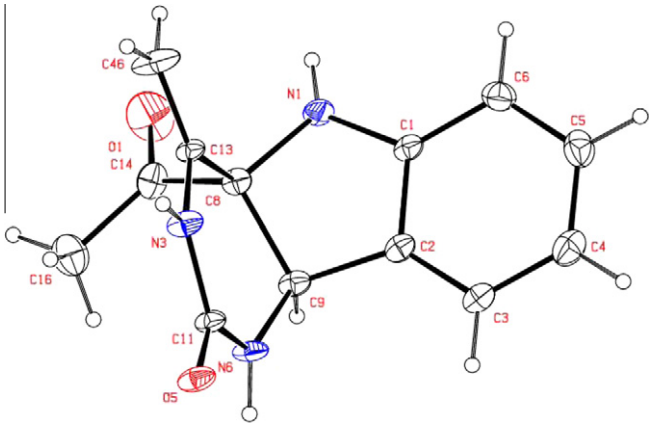
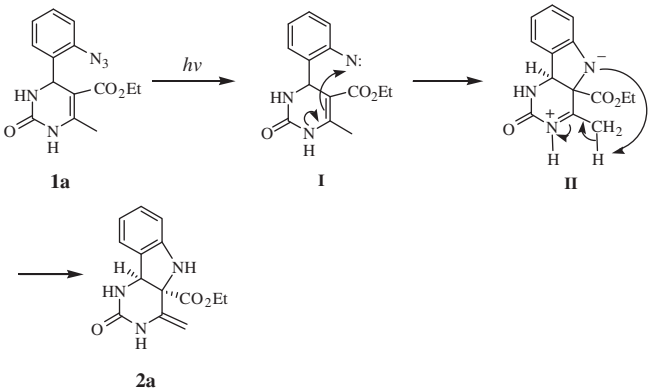


Figure 1. X-ray crystal structure of **2b**.



Scheme 2. Proposed mechanism for the photocyclization of **1a**.

depicted in Scheme 2. Photolysis or thermolysis of **1a** expels N_2 to produce a nitrene intermediate, and the cyclization occurs via nitrene **I** electrophilic attacking onto the α-position of the adjacent double bond of β-aminoacrylate to form a zwitterion **II** and subsequently the shift of a proton from methyl group to the nitrogen anion to give the product **2a**.

In conclusion, an efficient method for the synthesis of fused indoles, such as 1,2,3a,9b-tetrahydro-4-methylenepyrimidino [5,4-*b*]indol-2-ones and 1,3,5,6,7a,12b-hexahydroquinazolino[9,4-*b*]indol-2,7-dione in high yields via photochemical or thermal reaction of 4-(2-azidophenyl)-3,4-dihydropyrimidin-2-ones (**1a–j**) has been developed. The photolytic process is a little more facile than the thermal process.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.176.

References and notes

1. (a) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev*. **2007**, *36*, 1249; (b) Gritsan, N. P.; Platz, M. S. *Chem. Rev.* **2006**, *106*, 3844; (c) Braese, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188; (d) Scriven, E. F.; Turnbull, V. K. *Chem. Rev*. **1988**, *88*, 297.
2. (a) Minozzi, M.; Nanni, D.; Spagnolo, P. *Chem. Eur. J*. **2009**, *15*, 7830; (b) Lang, S.; Murphy, J. A. *Chem. Soc. Rev*. **2005**, *35*, 146; (c)*Organic Azides: Syntheses and Applications*; Bräse, S., Banert, K., Eds.; John Wiley and Sons Ltd: West Sussex, UK, 2001; (d) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
3. (a)*Azides and Nitrenes—Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: New York, 1984; (b)*The Chemistry of Halides, Pseudo—Halides and Azides, Part 1and 2*; Patai, S., Ed.; John Wiley and Sons, Ltd: Chichester, 1995.
4. Bayley, H. *Photogenerated Reagents in Biochemistry and Molecular Biology*; Elsevier: New York, 1983; (b) Wang, J. F.; Downs, W. D.; Cech, T. R. *Science* **1993**, *260*, 504.
5. (a) Condie, G. C.; Channon, M. F.; Ivory, A. J.; Kumar, N.; Black, StC. D. *Tetrahedron* **2005**, *61*, 4989; (b) Fresneda, P. M.; Molina, P. J.; Bleda, A. *Tetrahedron* **2001**, *57*, 2355; (c) Pelkey, E. T.; Gribble, G. W. *Tetrahedron Lett.* **1997**, *38*, 5603; (d) Fresneda, P. M.; Molina, P. S.; Angeles Saez, M. *Synlett* **1999**, 1651; (e) Kaszynski, P.; Dougherty, D. A. *J. Org. Chem.* **1993**, *58*, 5209; (f) Smith, P. A. S.; Rowe, C. D.; Hansen, D. W. *Tetrahedron Lett.* **1983**, *24*, 5169; (g) Garanti, L.; Zecchi, G. *J. Org. Chem.* **1980**, *45*, 4767; (h) Gairns, R. S.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1986**, 501.
6. (a) Morimoto, Y.; Matsuda, F.; Shimhama, H. *Tetrahedron* **1996**, *52*, 10609; (b) Morimoto, Y.; Matsuda, F.; Shirahama, H. *Tetrahedron Lett.* **1990**, *31*, 6031.
7. Shi, Z.; Ren, Y.; Li, B.; Lu, S.; Zhang, W. *Chem. Commun* **2010**, *46*, 3973.
8. (a) Giuseppe, R.; Luisa, M.; Gabriella, M.; Maria, M.; Valeria, P.; Loredana, S.; Angela, S. M.; Michela, B.; Piero, A.; Kenneth, P. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6200; (b) Giuseppe, R.; Luisa, M.; Fabrizio, M.; Alfredo, C.; Tiziana, M.; Ferdinando, N.; Maurizio, B.; Filippo, R.; Kenneth, P. M. *J. Med. Chem.* **2003**, *46*, 2877; (c) Merino, I.; Monge, A.; Font, M.; Martinez de Irujo, J. J.; Alberdi, E.; Santiago, E.; Prieto, I.; Lasarte, J. J.; Sarobe, P.; Borras, F. *Farmaco* **1999**, *54*, 255; (d) Santagati, A.; Longmore, J.; Guccione, S.; Langer, T.; Tonnel, E.; Modica, M.; Santagati, M.; Scolaro, L. Monsu; Russo, F. *Eur. J. Med. Chem.* **1997**, *32*, 973; (e) Santagati, N. A.; Caruso, A.; Cutuli, V. M. C.; Caccamo, F. *Farmaco* **1995**, *50*, 689; (f) Monge, A.; Martinez-Crespo, F. J.; Aranzazu Villanueva, M.; Font, M.; Santiageo, E.; Martinez de Irujo, J. J.; Alberdi, E.; Lopez-Unzu, M. J.; Cenarruzabeitia, E. *Arch. Pharm.* **1993**, *326*, 879; (g) Russo, F.; Romeo, G.; Guccione, S.; De Blasi, A. *J. Med. Chem.* **1991**, *34*, 1850.
9. (a) Sabitha, G.; Kumar Reddy, G. S. K.; Reddy, Ch. S.; Yadav, J. S. *Synlett* **2003**, 858; (b) Ryabukhin, S. V.; Plaskon, A. S.; Ostapchuk, E. N.; Volochnyuk, D. M.; Tolmachev, A. A. *Synthesis* **2007**, 417.
10. General procedure for the photochemical reactions: to 40 mL DMSO was added 2.0 mmol **1a**. The solution was distributed into two 25 mL Pyrex tubes and irradiated with a medium-pressure mercury lamp (500 W) at ambient temperature for appropriate time. The progree of the reaction was monitored by TLC at regular intervals. After **1a** were disappeared, the solvent removed in vacuo. The crude product was separated by silica gel column chromatography eluted with hexane/acetone 5:1 (v/v) to afford **2a** and further purified by recrystallization from ethanol.
Ethyl 4-methylene-2-oxo-2,3,4,4a,5,9b-hexahydro-1*H*-pyrimido[5,4-*b*]indole-4a-1carboxylate (**2a**): yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.95 (t, 3H, J = 7.2 Hz), 4.16 (q, 2H, J = 7.2 Hz), 4.36 (d, 2H, J = 9.6 Hz), 4.89 (d, 1H, J = 3.2 Hz), 6.61 (d, 1H, J = 8.0 Hz), 6.27–6.67 (t, 1H, J = 7.6 Hz), 6.79 (s, 1H), 7.02 (t, 1H, J = 7.6 Hz), 7.10 (d, 1H, J = 7.2 Hz), 7.49 (s, 1H), 8.97 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 13.87, 57.4, 61.5, 67.3, 89.8, 109.3, 118.2, 123.7, 128.1, 128.8, 141.7, 148.1, 151.6, 170.8; LC–MS (ESI): m/z requires 273, found ([M+H$^+$], 274); ESI-HRMS: m/z calcd for $C_{14}H_{15}N_3O_3 + H^+$ (M+H$^+$): 274.1186, found: 274.1182.
1,3,5,6,7a,12b-Hexahydroquinazolino[9,4-*b*]indol-2,7-dione (**2e**) yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24–2.31 (m, 1H), 2.32–2.42 (m, 1H), 2.53–2.61 (m, 1H), 3.14–3.21 (m, 1H), 4.94 (s, 1H), 5.27 (t, 1H, J = 4.4 Hz), 6.48 (d, 1H, J = 7.6 Hz), 6.63 (t, 1H, J = 7.6 Hz), 7.10 (d, 1H, J = 7.2 Hz), 7.62 (s, 1H), 9.00 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 25.4, 56.3, 72.4, 90.0, 109.36, 118.3, 123.5, 128.5, 128.6, 141.9, 147.9, 151.6, 204.4; LC–MS (ESI): m/z requires 255, found ([M+H$^+$], 256); ESI-HRMS: m/z calcd for $C_{14}H_{13}N_3O_2 + H^+$ (M+H$^+$): 256.1081, found: 256.1076.
11. Crystal data for compound **2b** (recrystallized from ethanol). $C_{13}H_{13}N_3O_2$, M_r = 243.26. Orthorhombic, a = 7.3985(16) Å, b = 11.859(3) Å, c = 26.749(6) Å, β = 90.00, V = 2346.9(9) Å^3, yellow plates, ρ = 1.377 g cm^{-3}, T = 296(2) K, space group $P2$ (1)/c, Z = 4, μ (Mo K_α) = 0.71073 mm^{-1}, $2\theta_{max}$ = 51.0°, 17008 reflections measured, 4349 unique (R_{int} = 0.0757) which were used in all calculation. The final w$R(F^2)$ was 0.1543 (for all data), R_1 = 0.0676. CCDC file no. 776808.