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Effects of substituent and catalyst on the intramolecular Povarov reaction—synthesis of chromenonaphthyridines

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ABSTRACT

2-(*N*-Alkenyl-*N*-aryl)aminochromone-3-carbaldehyde undergoes intramolecular Povarov reaction with aromatic amines in the presence of $Ph_3P{\cdot}HClO_4$ to produce chromenonaphthyridine. The effects of substituent and catalyst have been studied. The substituent on the alkenyl part of aminochromone controls the mode of reaction as well as the stereochemistry of the product.

[1,6]-Naphthyridine is a basic unit of many pharmaceutically important compounds. 7-Substituted-[1,6]-naphthyridine derivatives are potential tyrosine kinase inhibitors.[1] A series of [1,6]-naphthyridines exhibited potent activity against Human Cytomega lovirus.[2] 7-Carbamoyl-8-hydroxy derivatives act as novel inhibitors of HIV-I integrase in vitro and in infected cells.[3] 3-Oxadiazolyl-[1,6]-naphthyridine derivatives are useful as benzodiazedine receptor agonist.[4] Naphthyridines fused with various carbocyclic and heterocyclic rings display characteristic properties in multifarious pharmacological and chemotherapeutic activities. Some of them exhibit antimicrobial activities.[5]

Intramolecular imino-Diels–Alder reaction (Povarov reaction) has widely been studied in the last decade. Although the pioneering work of Povarov[6] was accomplished using $BF_3{\cdot}Et_2O$ as catalyst, other catalysts like $FeCl_3$, DDQ, $Ln(OTf)_3$,[7] $GdCl_3$,[8] $InCl_3$,[9] $SbCl_3$,[10] KSF-clay,[11] CAN,[12] $Yb(OTf)_3$,[13] $PPh_3{\cdot}HClO_4$ (TPP),[14] and glycerol[15] have also been employed. Intramolecular Povarov reaction is an important tool for the synthesis of two rings by a single operation and is utilised for the synthesis of tertahydroquinoline ring system fused with carbocycles[15] or different heterocycles like indolylpyrrole,[16] benzopyran.[14,17]

2-(*N*-Alkyl-/*N*-aryl)aminochromone-3-carbaldehyde (**1**) is a building block for the synthesis of different heterocycles.[18] 2-(*N*-Alkenyl-*N*-aryl)aminochromone-3-carbaldehyde (**2**) has been employed for the intramolecular [3+2] cycloaddition reaction via nitrone[19] or azomethine ylide[20] and intramolecular inverse electron demand [4+2] cycloaddition reaction.[21] The results of the reaction of compound **2** with aromatic amines **3** and the effects of substituent and catalyst on this reaction are reported herein.

With the intention of performing intramolecular imino-Diels–Alder (IIDA) reaction on **7** (**A** or **B**) (Scheme 2), a mixture of **2a** (0.25 mmol) and aromatic amine **3a** (0.25 mmol) was stirred in acetonitrile at room temperature. But, the reaction mixture produced a mixture of **4**[18b] and **5**[18f] along with unreacted **2a** (Table 1, entry 1) (Scheme 1). Formation of **5** may be explained by considering the nucleophilic substitution of 3°-amine moiety in **2a** by **3a** to form **4**. It reacts with the second molecule of **3a** to form the Schiff-base, which tautomerises to **5**. The mechanism demands two equivalents of **3a** to produce **5**. Indeed, compound **5** was isolated in good yield (80%) when 2 equiv of **3a** was employed.

In order to facilitate inverse electron demand IIDA reaction, the energy of $HOMO_{dienophile}$ in **7** was increased by introducing one methyl group into the alkenyl part of **2** by the alkenylation of **1** with crotyl bromide. But the reaction of **2b** with **3a** in CH_3CN again produced **5** (entry 2). Interestingly, use of **2c** (having one more methyl group in the dienophile) and **3a** yielded a mixture of **5** and a small amount of the desired product **6b** (entry 3) (Scheme 2). These results gave us an impetus to study this IIDA reaction more explicitly. Regarding the choice of solvent, CH_3CN was found to be the most effective solvent among MeOH, EtOH, toluene, DMF and CH_3CN. Realising the effect of increasing the energy of $HOMO_{dienophile}$ in the inverse electron demand IIDA reaction, we became interested to lower the energy of $LUMO_{heterodiene}$ by

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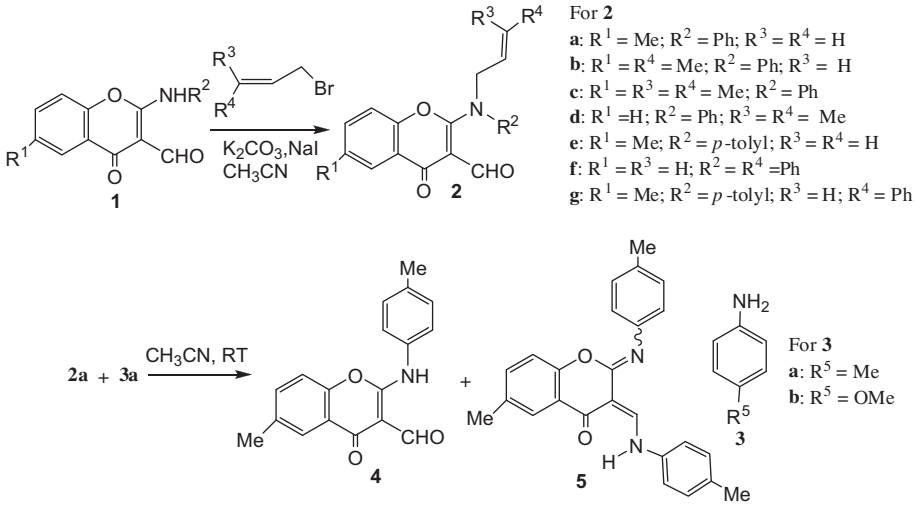
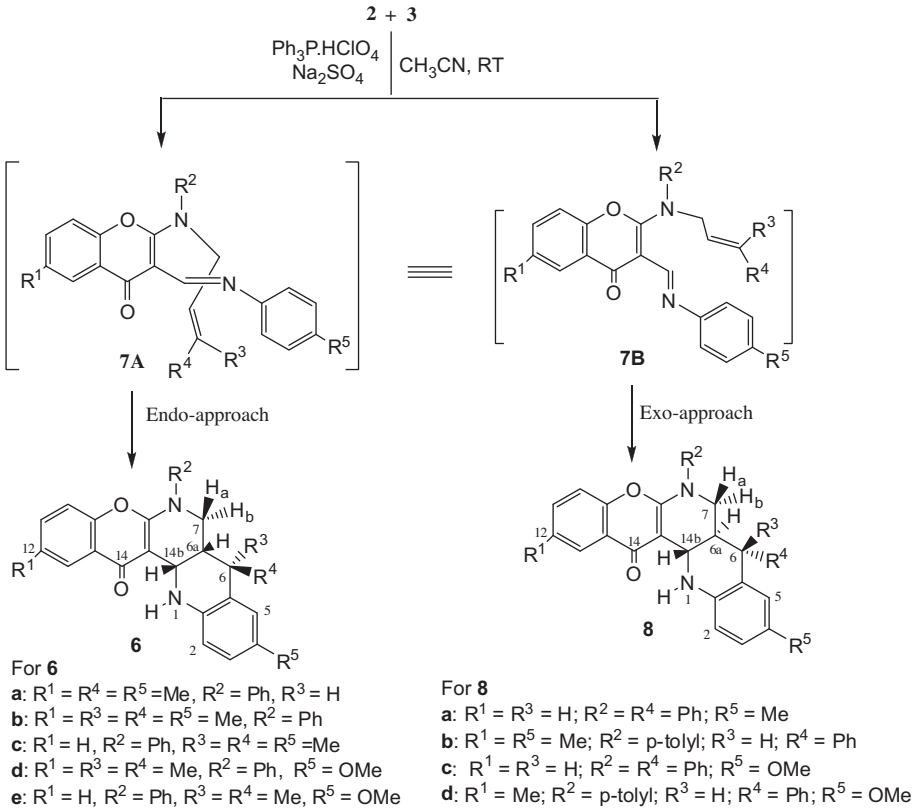


Scheme 1. Reaction between **2a** and **3a** in absence of catalyst.



Scheme 2. Reaction between **2** and **3** in presence of catalyst.

employing Lewis acid. With that intention a few catalysts like $FeCl_3$, $BF_3{\cdot}Et_2O$, $InCl_3$ and TPP were screened for the optimisation of this reaction. $FeCl_3$ showed some detrimental effect (entry 4), which may be due to complexation between **2c** and $FeCl_3$. $BF_3{\cdot}Et_2O$ gave poor yield of **6b** (entry 5), but $InCl_3$ gave a moderate yield (53%) of **6b** in 15 h (entry 6). Use of TPP shortens the reaction time with a little improvement in yield of **6b**[22] (entry 7).

Catalyst loading of TPP was standardised based on the reaction of **2c** and **3a** in acetonitrile. It was observed that use of 40 mol % of TPP gave the best result (entries 7–10). Use of 10 mol % of TPP gave a mixture of **5** and **6b** (entry 8). A few more reactions for the synthesis of **6** having different substituent on chromone **2** and amine **3** were performed (entries 11–13). To check the effectiveness of the catalyst, TPP (40 mol %) was employed into an equimolar mixture of **2b** and **3a** in CH_3CN. After stirring for 20 h, the reaction mixture produced **5** as the major product and small amount of **6a** (5%) (entry 14). When the same reaction using **2e** and **3a** was carried out, $InCl_3$ or TPP failed to cause IIDA reaction and compound **5** along with unreacted material **2e** was isolated (entries 15 and 16). These results clearly indicate that the individual effect of increasing the energy of $HOMO_{dienophile}$ or decreasing the energy of $LUMO_{heterodiene}$ is not sufficient for **7** to take part in

Table 1
Results of the reaction between **2** and **3** under different conditions

Entry	2	3	Catalyst (mol %)	Time (h)	Product	Yield (%)	Mp (°C)
1	**2a**	**3a**	—	20	**5**[a]	29[b]	214–216[18f]
2	**2b**	**3a**	—	15	**5**	25[b]	212–214
3	**2c**	**3a**	—	30	**5**	15[c]	214–216
					6b	13	154–156
4	**2c**	**3a**	$FeCl_3$(20)	5	**6b**	06	154–156
5	**2c**	**3a**	$BF_3{\cdot}Et_2O$	4	**6b**	26	154–156
6	**2c**	**3a**	$InCl_3$ (20)	15	**6b**	53	154–156
7	**2c**	**3a**	TPP (20)	8	**6b**	57	154–156
8	**2c**	**3a**	TPP (10)	12	**6b**	45	154–156
					5	05	214–216
9	**2c**	**3a**	TPP (40)	6	**6b**	87	154–156
10	**2c**	**3a**	TPP (60)	6	**6b**	85	154–156
11	**2d**	**3a**	TPP (40)	6	**6c**	89	198–200
12	**2c**	**3b**	TPP (40)	6	**6d**	90	150–154
13	**2d**	**3b**	TPP (40)	6	**6e**	58	196–198
14	**2b**	**3a**	TPP (40)	20	**5**	30[c]	214–216
					6a	05	160–162
15	**2e**	**3a**	$InCl_3$(20)	15	**5**	25[b]	214–216
16	**2e**	**3a**	TPP (40)	15	**5**	22[b]	214–216
17	**2f**	**3a**	TPP (40)	5	**8a**	63	262–264
18	**2g**	**3a**	TPP (40)	6	**8b**	65	170–172
19	**2f**	**3b**	TPP (40)	5	**8c**	77	250–252
20	**2g**	**3b**	TPP (40)	6	**8d**	58	218–220

Ar = *p*-C_6H_4(Me).
[a] Use of 2 equiv of **3a** produced 80% of **5**.
[b] 10–15% of **2** was recovered and trace amount of **4** was detected.
[c] Very small amount of **4** was also isolated.

IIDA reaction but their combined effect led to the desired result. Structure of **6** was assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.[23] The *cis* stereochemistry of CD-ring juncture in **6** was assigned on the basis of small coupling constant value (J = 2.7 Hz) at δ 5.13 for C_{14b}–H.

The above methodology was then extended with **2f** and **2g**. An equimolar mixture of **2f** or **2g** and **3a** or **3b** in CH_3CN was stirred at room temperature for 5–6 h in the presence of TPP (40 mol %) and Na_2SO_4 to produce **8a–d** in moderate yields (entries 17–20). The noticeable thing is that the CD-ring juncture in **8** is *trans* in nature, which is observed from the large coupling constant value (J = 9.9 Hz) at δ 4.6 for C_{14b}–H.

Formation of **6** and **8** may be rationalised as follows: **2** reacts with **3** to form the aldimine **7**, which attains conformation **7A** or **7B** for performing [4+2] cycloaddition reaction. *Endo*-approach of dienophile in **7A** is favoured when R^4 = Me to form **6**, whereas *exo*-approach in **7B** led to the formation of *trans*-fused product **8** when R^4 = Ph (Scheme 2). In the *exo*-approach (**7B**) (R^4 = Ph), this phenyl group becomes *endo* to the heterodiene and is supposed to exert additional secondary bonding interaction.

In conclusion, we have reported a substituent- and catalyst-controlled intramolecular imino-Diels–Alder reaction involving 2-(*N*-alkenyl-*N*-aryl)aminochromone-3-carbaldehyde and aryl amines, which led to the synthesis of hitherto unreported chromenonaphthyridines.

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References and notes

1. Thompson, A. M.; Hollis Shoalter, H. D.; Denny, W. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1843–1852.
2. Chan, L.; Jin, H.; Stefanac, P.; Lavallee, J. F.; Falardeau, G.; Wang, W.; Bedard, J.; May, S.; Yuen, L. *J. Med Chem.* **1999**, *42*, 3023–3025.
3. Melamed, J. Y.; Eqbertson, M. S.; Varga, S.; Vacca, J. P.; Moyer, G.; Gabryelski, L.; Felock, P. J.; Stillmock, K. A.; Witmer, M. V.; Schleif, W. A.; Hajuda, D. J.; Leinard, Y.; Jin, L.; Ellis, J. D.; Young, S. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5307–5310.
4. Furukawa, K.; Odai, O.; Ohno, K.; Oka, M.; Tominaqa, Y. U.S. Patent, **1994**, 5367078.
5. Suresh, T.; Dhanabal, T.; Nandha Kumar, R.; Mohan, P. S. *Indian J. Chem.* **2005**, *44B*, 2375–2379. and refernces therein.
6. Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656–670.
7. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070.
8. Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462–6467.
9. Zhang, J.; Li, C.-J. *J. Org. Chem.* **2002**, *67*, 3969–3971.
10. Maiti, G.; Kundu, P. *Tetrahedron Lett.* **2006**, *47*, 5733–5736.
11. Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Reddy, P. S. R. *Tetrahedron Lett.* **2002**, *43*, 3853–3856.
12. (a) Sabitha, G.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 3589–3593; (b) Sridharan, V.; Avendano, C.; Menendez, J. C. *Tetrahedron* **2007**, *63*, 673–681.
13. Kudale, A. K.; Kendall, J.; Miller, D. O.; Collins, J. L.; Bodwell, G. J. *J. Org. Chem.* **2008**, *73*, 8437–8447.
14. Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2003**, *44*, 3653–3657.
15. Nascimento, J. E. R.; Barcellos, A. M.; Sachini, M.; Perin, G.; Lenardao, E. J.; Alves, D.; Jacob, R. G.; Missau, F. *Tetrahedron Lett.* **2011**, *52*, 2571–2574.
16. Manian, R. D. R. S.; Jayashankaran, J.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 4139–4142.
17. (a) Ramesh, S.; Gaddam, V.; Nagarajan, R. *Synlett* **2010**, 757–760; (b) Majumdar, K. C.; Ponra, S.; Taher, A. *Synthesis* **2011**, 463–468.
18. (a) Singh, G.; Singh, R.; Girdhar, N. K.; Ishar, M. P. S. *Tetrahedron* **2002**, *58*, 2471–2480; (b) Bandyopadhyay, C.; Sur, K. R.; Patra, R.; Banerjee, S. *J. Chem. Res. (S)* **2003**, 459–460. *J. Chem. Res.* (*m*), **2003**, 847–856; (c) Singh, G.; Singh, G.; Ishar, M. P. S. *Helv. Chim. Acta* **2003**, *86*, 169–180; (d) Singh, G.; Singh, L.; Ishar, M. P. S. *Tetrahedron* **2002**, *58*, 7883–7890; (e) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *Tetrahedron Lett.* **2009**, *50*, 3966–3969; (f) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *Indian J. Chem., Sect. B* **2009**, *48*, 1447–1452; (g) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *J. Heterocycl. Chem.* **2010**, *47*, 973–981; (h) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *J. Chem. Res.* **2011**, 84–86; (i) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *Tetrahedron Lett.* **2011**, *52*, 1946–1948; (j) Maiti, S.; Mallick, S.; Panja, S. K.; Pal, C.; Bandyopadhyay, C. *Synlett* **2011**, 2001–2004.
19. Singh, G.; Ishar, M. P. S.; Gupta, V.; Singh, G.; Kalyan, M.; Bhella, S. S. *Tetrahedron* **2007**, *63*, 4773–4778.
20. Maiti, S.; Lakshmykanth, T. M.; Panja, S. K.; Mukhopadhyay, R.; Datta, A.; Bandyopadhyay, C. *J. Heterocycl. Chem.* **2011**, *48*, 763–768.
21. Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *Tetrahedron* **2010**, *66*, 7625–7632.
22. *General procedure for the synthesis of* **6**: A solution of **2** (R^3 = R^4 = Me) (0.25 mmol) and **3** (0.25 mmol) in dry CH_3CN (5 mL) containing anhydrous Na_2SO_4 (355 mg, 2.5 mmol) was stirred with TPP (36 mg, 40 mol %) at room temperature for appropriate time (Table 1). After completion (TLC), the reaction mixture was poured into water (50 mL). The resulting turbid solution was extracted with EtOAc. The EtOAc solution was dried over Na_2SO_4 and purified by column chromatography over silica gel (100–200) to obtain **6** in good yield using benzene as eluent.
23. 4,6,6,12-Tetramethyl-8-phenyl-1,6,6a,7,8,14b-hexahydro-benzo[*b*]chromeno[2,3-*h*][1,6]naphthyridin-14(14*H*)-one (**6b**): IR (KBr) ν_{max}: 3350, 2968, 2912, 2866, 1611, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.39 (3 H, s, 6-CH_3), 1.43 (3 H, s, 6-CH_3), 1.99–2.05 (1H, m, 6a-H), 2.23 (3 H, s, 4-CH_3), 2.42 (3 H, s, 12-CH_3), 3.60 (1H, dd, J = 11.7, 3.9 Hz, 7-H_a), 3.73 (1H, dd, J = 12.0, 11.7 Hz, 7-H_b), 4.46 (1H, br s, exchangeable, 1-H), 5.13 (1H, d, J = 2.7 Hz, 14b-H), 6.38 (1H, d, J = 8.1 Hz, 2-H), 6.82 (1H, br d, J = 8.1 Hz, 3-H), 6.93 (1H, br s, 5-H), 6.95 (1H, d, J = 8.1 Hz, 10-H), 7.28–7.36 (4H, m, ArH), 7.40–7.46 (2H, m, ArH), 7.98 (1H, br s, 13-H); ^{13}C NMR ($CDCl_3$) δ: 20.7, 20.8, 25.9, 33.8, 34.4, 41.2, 41.9, 49.6, 98.8, 114.0, 116.1, 122.6, 125.0, 125.7, 125.9, 126.0, 126.5, 126.8, 127.9, 129.1, 132.9, 134.4, 138.3, 141.8, 151.3, 158.3, 175.0; Mass *m*/*z*: 437 (M^++H), 459 (M^++Na); Anal. calcd for $C_{29}H_{28}N_2O_2$: C, 79.79; H, 6.46; N, 6.42%. Found: C, 79.63; H, 6.39; N, 6.36%.