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SYNTHESIS OF 1*H*-IMIDAZO[4,5-*c*]QUINOLIN-4(5*H*)-ONE VIA PALLADIUM-CATALYZED CYCLIZATION OF N-(2-BROMOPHENYL)-1*H*-IMIDAZOLE-4-CARBOXAMIDE

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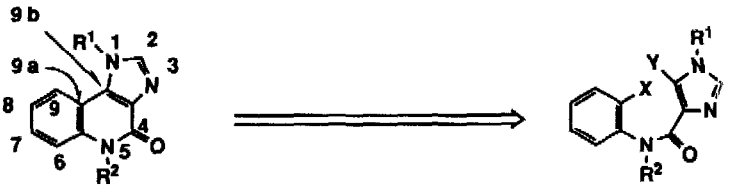
ABSTRACT: A new heterocycle, 5-butyl-1-methyl-1*H*-imidazo[4,5-c]quinolin-4(5*H*)-one has been synthesized using palladium-catalyzed cyclization. A yield of the cyclization was optimized by changing base, additive and reaction temperature.

1*H*-Imidazo[4,5-*c*]quinolin-4(5*H*)-one derivatives **A** has been shown to exhibit potent antiasthmatic activities[1]. This discovery has stimulated our efforts to devise their efficient and direct chemical syntheses of pharmacologically active structural analogues.



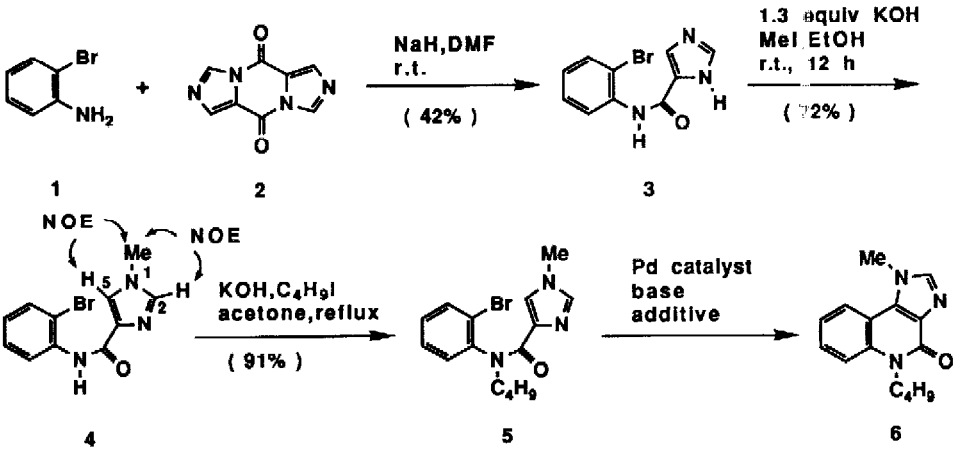
A **B**

Retrosynthetic analysis suggested that simple disconnection of the single bond C_{9a}-C_{9b} to N-phenyl-1*H*-imidazole-4-carboxamide derivative **B**, might be appropriate. The key step in this approach would be the intramolecular phenyl-imidazole coupling reaction. The intramolecular diaryl couplings to tricyclic compounds have been carried out by catalytic amounts of palladium[2]. We report here a new synthetic route to tricyclic heterocycles using this method.

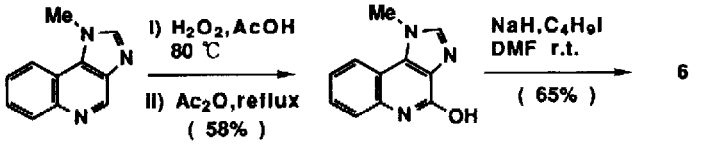
As shown in Scheme 1, reaction of 2-bromoaniline **1** with diimidazo[3,4-*a*;3',4'-*d*]piperazine-2,5-dione **2**[3] gave N-(2-bromophenyl)-imidazole-4(5)-carboxamide **3**[4]. Regioselective methylation of **3** was achieved with 1equiv MeI to give **4**[5]. Observation of NOEs between 1-Me and 2-H, and between 1-Me and 5-H indicated the location of the methyl group as illustrated in **4**[6]. Butylation of **4** gave a sole product **5**[8]. Ames developed the cyclization method by intramolecular dehydrohalogenative coupling using catalytic amounts of palladium (II) salts

under basic conditions[2]. This reaction was applied for our ring system. The treatment of **4** with catalytic amounts of palladium [30 mol % $Pd(OAc)_2$, 1.3 equiv Na_2CO_3, N,N-dimethylacetamide (DMA), 170℃, 3h] gave no cyclized product, the starting material **4** being recoverd. On the other hand, when **5** was used as a precursor, the palladium-catalyzed cyclization occurred cleanly to give the corresponding tricyclic heterocycle, 5-butyl-1-methyl-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **6**[9] in a 60% yield . The chemical structure of **6** was consistent with its spectral data and was confirmed through the alternative synthesis as shown in Scheme 2[1].

Scheme 1



Scheme 2



Optimum conditions of the palladium-catalyzed cyclization were examined (Table 1). Amounts of palladium acetate could be decreased to 10 mol % (entry 3 *vs.* 2). The temperature was varied from 80℃ to 170℃. Cyclization needed heating at least at 150℃ (entry 2 *vs.* 1, 3 *vs.* 5, 9 *vs.* 8). Palladium acetate was more favourable than other palladium agents in this reaction (entry 3 *vs.* 6 and 7). Addition of tetrabutylammonium chloride (the phase transfer agent)[10] improved the yield of **6** (entry 3 *vs.* 9, 4 *vs.*10, 5 *vs.* 8). Various bases were employed and the best was found to be sodium hydrogen carbonate (entry 4 *vs.* 3, entry 9 *vs.* 10, 11, 12)[11]. DMAP suppressed the reaction and gave the starting material (entry 12). Reaction in butan-1-ol gave only the reduced product **9** in a 78% yield (entry 14). A high yield of **6** was observed at 150℃ in DMA in the presence of catalytic amounts of palladium acetate (10 mol %), sodium hydrogen carbonate, and tetrabutylammonium chloride (entry 10).

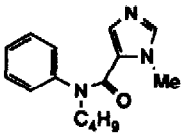


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Table 1. Palladium-catalyzed cyclization of **5**

Entry	Solvent	Catalyst	Mol %	Base	Additive	Temp (℃)	Time (h)	Yield[a] of **6** (%)	Starting material **5** (%)
1	DMA	$Pd(OAc)_2$	30	Na_2CO_3[b]	–	170	3	60	–
2	DMA	$Pd(OAc)_2$	30	Na_2CO_3[b]	–	150	7	60	–
3	DMA	$Pd(OAc)_2$	10	Na_2CO_3	–	150	24	60	–
4	DMA	$Pd(OAc)_2$	10	$NaHCO_3$[c]	–	150	24	73	–
5	DMA	$Pd(OAc)_2$	10	Na_2CO_3	–	80	65	22	46
6	DMA	$PdCl_2(CH_3CN)_2$	10	Na_2CO_3	–	150	24	42	–
7	DMA	$Pd(PPh_3)_4$	10	Na_2CO_3	–	150	24	50	–
8	DMA	$Pd(OAc)_2$	10	Na_2CO_3	*n*-Bu_4NCl[d,e]	80	120	43	24
9	DMA	$Pd(OAc)_2$	10	Na_2CO_3	*n*-Bu_4NCl	150	24	70	–
10	DMA	$Pd(OAc)_2$	10	$NaHCO_3$	*n*-Bu_4NCl	150	24	83	–
11	DMA	$Pd(OAc)_2$	10	DBU[c]	*n*-Bu_4NCl	150	24	44	–
12	DMA	$Pd(OAc)_2$	10	DMAP[c]	*n*-Bu_4NCl	150	24	–	69
13	DMF	$Pd(OAc)_2$	10	$NaHCO_3$	*n*-Bu_4NCl	150	24	63	12
14	Butan-1-ol	$Pd(OAc)_2$	10	$NaHCO_3$	*n*-Bu_4NCl	150	24	–	–
15	*n*-PrCN	$Pd(OAc)_2$	10	$NaHCO_3$	*n*-Bu_4NCl	150	24	13	24

a. Isolated yields.; b. 1.3 mol equiv; c. 2.5 mol equiv; d. 1.0 mol equiv; e. 1.0 hydrate. DBU:1,8-diazabicyclo[5,4,0]undec-7-ene. DMAP:4-dimethylaminopyridine.

In conclusion, a convenient and regioselective route to a new heterocycle, 1*H*-Imidazo[4,5-*c*]quinolin-4(5*H*)-one has been developed by using palladium-catalyzed cyclization as a key step. Further extensions and applications of these methods to other tricyclic heterocycles are currently under study.

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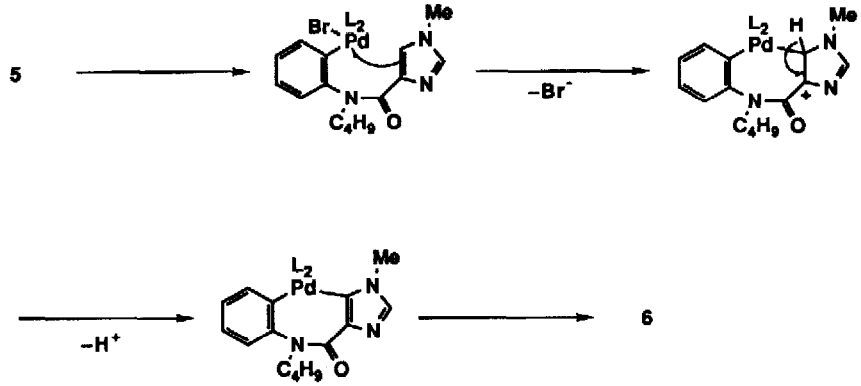
References and Notes:

1. F. Suzuki, T. Kuroda, Y. Nakasato, K. Ohmori, and H. Manabe, U.S. Patent 4 994 468, 1991.
2. D. E. Ames and A. Opalko, *Tetrahedron*, *40*, 1919 (1984).
3. S. Kasina and J. Nematollahi, *Synthesis*, 162 (1975).
4. **3**; H^1 NMR ($CDCl_3$ + CD_3OD) δ 8.40 (dd, 1H, *J* = 8, 2 Hz), 7.77 (d, 1H, *J* = 1 Hz), 7.67 (d, 1H, *J* =

1 Hz), 6.80-7.70 (m, 3H); IR (KBr) υ 1665, 1578, 1522 cm^{-1}; MS (m/e) 265 (M^+), 267; mp 184-187 ℃.

5. **4**; H^1 NMR (DMSO-d_6) δ 9.60 (br s, 1H), 8.38 (dd, 1H, J = 8, 2 Hz), 7.88 (d, 1H, J = 1 Hz), 7.79 (d, 1H, J = 1Hz), 7.68 (dd, 1H, J = 8, 2 Hz), 7.41 (br t, 1H, J = 8 Hz), 7.04 (br t, 1H, J = 8 Hz), 3.74 (s, 3H); IR (KBr) υ 1674, 1557, 1506 cm^{-1}; MS (m/e) 279 (M^+), 281; mp 147-149 ℃. The regiochemistry of methyl group in imidazole was also confirmed by spectroscopic analysis of the following cyclized product **6**[9].
6. Methylation of N-phenylimidazole-4(5)-carboxamide was reported to yield N-phenyl-1-methylimidazole-4-carboxamide. Location of the above methyl group was assigned from its chemical shift[7].
7. E. P. Papadopoulos, *J. Org. Chem.*, *42*, 3925 (1977).
8. **5**; H^1 NMR ($CDCl_3$) δ 7.62 (d, 1 H, J = 8 Hz), 6.70-7.37 (m, 5H), 3.33-4.28 (m, 2H), 3.53 (s, 3H), 1.50-1.72 (m, 2H), 1.23-1.45 (m, 2H), 0.91 (t, 3H, J = 7 Hz); IR (KBr) υ 1633, 1545 cm^{-1}; MS (m/e) 335 (M^+), 337; mp 90-92 ℃.
9. **6**; H^1 NMR (DMSO-d_6) δ 8.20 (br d, 1H, J = 8 Hz), 8.10 (s, 1H), 7.55-7.65 (m, 2H), 7.34 (br t, 1H, J = 8 Hz), 4.34 (t, 2H, J = 7 Hz), 4.17 (s, 3H), 1.55-1.64 (m, 2H), 1.37-1.45 (m, 2H), 0.94 (t, 3H, J = 7 Hz); IR (KBr) υ 1645cm^{-1}; MS (m/e) 255 (M^+); mp 208-209 ℃.
10. T. Jeffery, *J. Chem. Soc., Chem.Commun.*, 1287 (1984).
11. This cyclization is speculated to proceed via palladation followed by nucleophilic displacement of bromide ion by the imidazole ring and elimination of Pd(0)[12]. Bases might accelerate the deprotonation process.



12. D. E. Ames and D. Bull, *Tetrahedron*, *38*, 383 (1982).

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