ONE-POT SYNTHESIS OF 1,10-DIHYDRO-2*H*-IMIDAZO[3,4-*a*]-QUINAZOLIN-1-ONES FROM 3-ACYL-1,2-DIHYDROCINNOLINE-1,2-DICARBOXIMIDES

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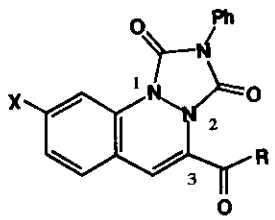
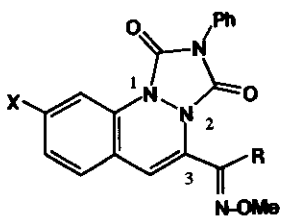
Abstract- 3-Substituted 1,10-dihydro-2*H*-imidazo[3,4-*a*]quinazolin-1-ones were prepared from 3-acyl-1,2-dihydrocinnoline-1,2-dicarboximides and piperidine in DMSO in moderate yields *via* Michael additions, skeletal rearrangements, and subsequent decarboxylation.

Utilization of hydrazodicarboximides (urazoles) in organic syntheses has been limited so far only to preparations of azoalkanes,[1] α-diketones,[2] and triazines.[3] This restricted use is attributed, in part, to thermal and photochemical stability of the urazole ring.[1] However, the versatile urazoles bearing a triazo skeleton appear to provide potential usefulness as the starting source for syntheses of heterocyclic compounds. Our strategy for opening of the urazole ring under mild conditions is to utilize participation of double bonds (carbon-carbon, carbon-oxygen, carbon-nitrogen) adjacent to the urazole ring. Along this line, we have reported one-pot syntheses of a variety of intricate heterocyclic compounds from urazoles (**1**) and (**2**), including hetero analogues of angular triquinanes (tricyclo[6.3.0.$0^{1,5}$]undecene skeleton),[4] hetero[4.3.3]propellanes,[5] cyanoindoles,[6] triazinoindoles,[7] and triazinoindolines.[7] As a part of our investigations to explore the synthetic potential of the urazoles in organic syntheses, we describe herein one-pot construction of an imidazo[3,4-*a*]quinazolin-1-one skeleton based on a piperidine-assisted rearrangement of urazole (**1**) and a subsequent decarboxylation.

In a typical experiment, an excess of piperidine was added to a DMSO solution of yellow urazole [3-acetyl-7-methoxy-1,2-dihydrocinnoline-*N*-phenyl-1,2-dicarboximides] (**1a**), the solution turning colorless in 1 h at 25℃. After acidification with hydrochloric acid and then neutralization with sodium bicarbonate, the solution was



1



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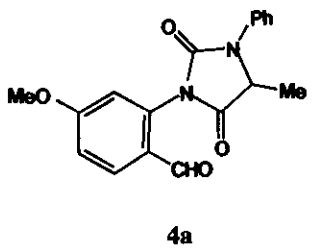
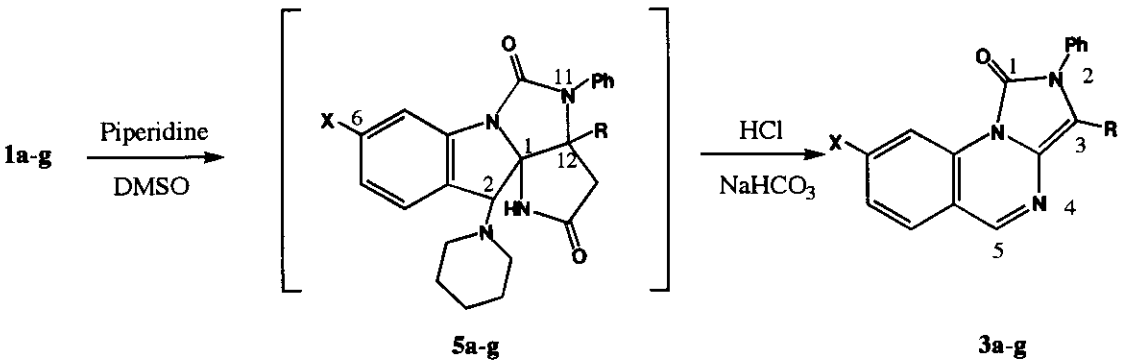


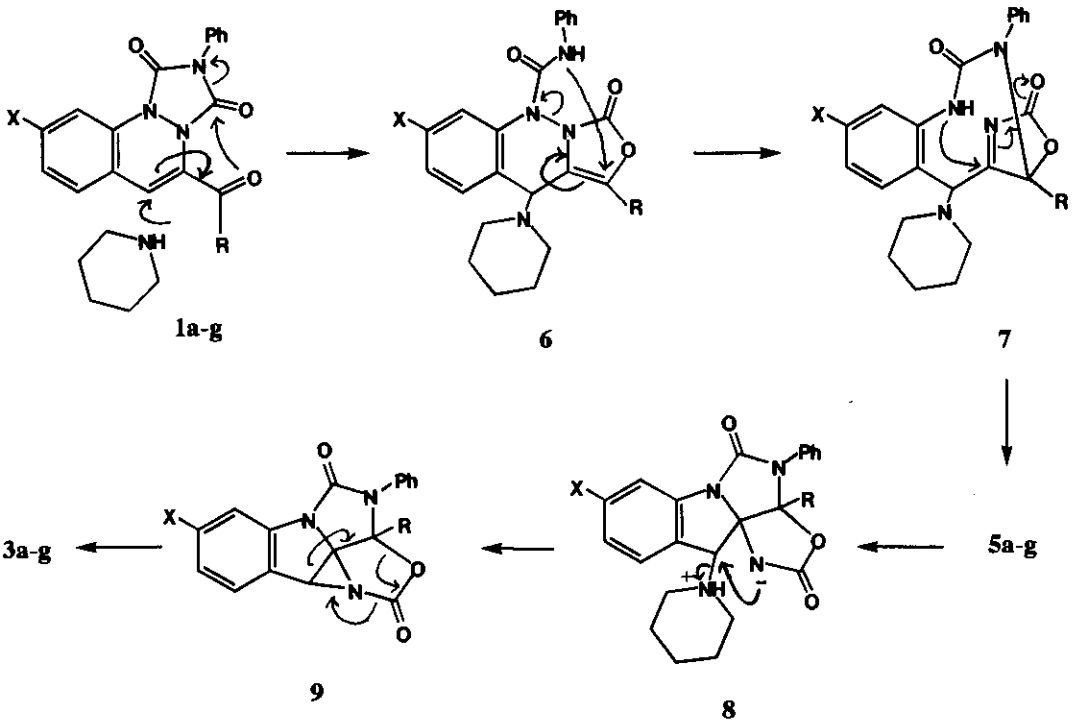
4a

X=OMe, H R=alkyl, phenyl



5a-g

3a-g



1a-g

6

7

5a-g

8

9

3a-g

Scheme 1

Table 1. Preparations of dihydroimidazoquinazolinones (**3**) from urazoles (**1**).

Starting compound (**1**)			Product (**3**)	Yield (%)
	X	R		
1a	OMe	Me	**3a**	28
1b	OMe	Ph	**3b**	54
1c	OMe	Furyl(2-)	**3c**	54
1d	OMe	*p*-MeO-Ph-CH=CH-	**3d**	85
1e	H	Ph	**3e**	63
1f	H	Ph-CH=CH-	**3f**	83
1g	H	4-MeO-naphthyl(1-)	**3g**	63

allowed to stand overnight at 25℃ to give orange dihydroimidazoquinazolinone (**3a**) in 28% yield. The structure of **3a** was characterized by ^{1}H-NMR, ^{13}C-NMR, elemental analysis, and a chemical transformation. In the mass spectrum of **3a** the parent ion appeared at *m/z* 305, indicating that one molecule of carbon dioxide had eliminated from **1a**. The ^{1}H-NMR spectrum showed two methyl singlets at δ 2.24 and δ 3.89, and a singlet due to an iminomethine group at δ 8.14. The ^{13}C-NMR showed two methyl quartets at δ 8.7 and δ 55.8, a doublet due to an iminomethine group at δ 148.9, seven sp^2 singlets including a resonance due to a carbonyl carbon of cyclic urea at δ 147.5,[4] while the carbonyl carbon of the acetyl group of **1a** had disappeared. Elemental analysis satisfied the proposed structure. Furthermore, hydrolysis of **3a** with hydrochloric acid in aqueous DMSO readily occurred to give a ketone (**4a**) in 45% yield. The structure of **4a** was also characterized by the spectral data and elemental analysis. Two proton resonances at δ 3.94 and δ 9.89 showed the presence of the methoxyl and formyl groups. Resonances due to an ethylidene group appeared at δ 4.79 (q) and δ 1.63 (d). The ^{13}C-NMR spectrum and elemental analysis also satisfied the structure of **4a**. These results indicate that **3a** has a dihydroimidazoquinazolinone structure. Similarly, other substituted urazoles (**1b-g**) gave the corresponding dihydroimidazoquinazolinones (**3b-g**) in 54-85% yields (See Table 1).

In order to detect the reaction intermediate, the reactions with piperidine using **1b-e** were pursued by ^{1}H-NMR

spectroscopy in DMSO-d_6. In the case of **1e**, a singlet proton signal appeared at δ 4.25 in place of disappearance of a singlet due to an olefinic proton (δ 6.47) of **1e**. On the basis of the spectral comparison with the previously reported compounds,[4] this intermediate was found to be a piperidine-incorporated tricyclic oxazolidinone derivative (**5e**), in which a newly appearing proton signal was assigned to 2-H. The structure of isolated **5e** was fully characterized by spectral data and elemental analysis. Furthermore, **5e** in aqueous DMSO afforded **3e** in 74% yield by maintaining at 50℃ for 5 h. Similar piperidine-assisted transformations from **1b-d** to corresponding **5b-d** were confirmed by means of ^{1}H-NMR. However, attempts to isolate **5c** and **5d** failed because of ready transformations to **3c** and **3d** during the purification procedures.

The following consecutive reaction mechanism would be surmised to account for the formation of dihydroimidazoquinazolinones (Scheme 1). The initial reaction involves a Michael addition of piperidine to a polar enone substructure of the urazole (**1**). Opening of the urazole ring *via* intermediates (**6**) and (**7**) accompained with nitrogen-nitrogen bond cleavage gives the tricyclic oxazolidinone(**5**),[4] which would change into **3** *via* intermediates (**8**) and (**9**).[8,9]

EXPERIMENTAL

Instrument and materials. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Hitachi R-1900 spectrometer in a $CDCl_3$ solution unless otherwise stated, with TMS as an internal reference. IR spectra and MS spectra were measured on a Shimadzu R-460 spectrophotometer and a Shimadzu QP-2000A spectrometer, respectively. 3-Acyl-1,2-dihydrocinnoline-*N*-phenyl-1,2-dicarboximides (**1a-g**) were prepared by the addition-elimination reactions of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione with benzylidene ketones according to the previous paper.[10]

General procedure for dihydroimidazoquinazolinones (3a-g). An excess of piperidine was added to a DMSO (10 mL) solution of dicarboximide (**1a-g**) (0.50 mmol), the solution being stirred for 1 h at 25℃. After acidification with 4% hydrochloric acid and then neutralization with saturated sodium bicarbonate solution, the solution was allowed to stand overnight at 25℃ or 50 ℃. The precipitates were collected by suction and recrystallized from an appropriate solvent.

1,10-Dihydro-8-methoxy-3-methyl-2-phenyl-2H-imidazo[3,4-a]quinazolin-1-one (3a). Orange plates from EtOH; mp 194-195℃; ^{1}H-NMR δ : 2.24 (s, 3H), 3.89 (s, 3H), 6.78 (dd, J =8.6 and 2.4 Hz, 1H), 7.25 (d, J =8.6 Hz, 1H), 7.35-7.51 (m, 5H), 8.14 (s, 1H, 5H), 8.86 (d, J =2.4 Hz, 1H); ^{13}C-NMR δ : 8.7 (q), 55.8 (q), 99.7 (d), 110.1 (s), 112.3 (d), 113.1 (s), 127.2 (s), 127.5 (d), 128.3 (d), 128.9 (d), 129.3 (d), 134.0 (s),

137.3 (s), 147.5 (s, CO), 148.9 (d, C=N), 163.2 (s); MS *m/z* 305 (M^+); IR (KBr) 1685, 1601 cm^{-1}. Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N,13.76. Found: C, 70.67; H, 5.05; N,13.70.

*1,10-Dihydro-8-methoxy-2,3-diphenyl-2H-imidazo[3,4-a]quinazolin-1-one (**3b**).* Orange needles from EtOH; mp 244-245°C; ^{1}H-NMR δ : 3.89 (s, 3H), 6.81 (dd, J=8.2 and 2.3 Hz, 1H), 7.16-7.50 (m, 11H), 8.04 (s, 1H, 5-H), 8.52 (d, J=2.3 Hz, 1H); ^{13}C-NMR δ : 55.8 (q), 99.9 (d), 112.9 (d), 113.5 (s), 126.6 (s), 127.2 (d), 127.4 (d), 127.6 (d), 127.7 (s), 128.1 (d), 128.8 (d), 128.9 (d), 129.0 (s), 134.8 (s), 137.3 (s), 147.2 (s, CO), 151.3 (d, C=N), 163.5 (s); MS *m/z* 367 (M^+); IR (KBr) 1697, 1601 cm^{-1}. Anal. Calcd for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44. Found: C, 75.07; H, 4.58; N, 11.44.

*3-Furyl-1,10-dihydro-8-methoxy-2-phenyl-2H-imidazo[3,4-a]quinazolin-1-one (**3c**).* Orange needles from acetone; mp 238-240°C; ^{1}H-NMR δ : 3.90 (s, 3H), 6.12 (dd, J=3.5 and 0.6 Hz, 1H), 6.34 (dd, J=3.5 and 1.8 Hz, 1H), 6.83 (dd, J=8.7 and 2.4 Hz, 1H), 7.30-7.60 (m, 7H), 8.15 (s, 1H, 5-H), 8.50 (d, J=2.4 Hz, 1H); ^{13}C-NMR δ : 55.8 (q), 99.8 (d), 109. 7(d), 111.0 (d), 113.2 (s), 126.4 (s), 127.6 (d), 128.2 (s), 129.0 (d), 129.1 (d), 134.8 (s), 137.1 (s), 142.5 (d), 147.7 (s, CO), 151.6 (d, C=N), 163.7(s); MS *m/z* 357 (M^+); IR (KBr) 1696, 1606 cm^{-1}. Anal. Calcd for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.68; H, 4.33; N, 11.82.

*1,10-Dihydro-8-methoxy-3-(4-methoxybenzylidene)-2-phenyl-2H-imidazo[3,4-a]quinazolin-1-one (**3d**).* Red needles from acetone; mp 226-228°C; ^{1}H-NMR δ : 3.77 (s, 3H), 3.89 (s, 3H), 6.70-6.90 (m, 5H), 7.18-7.60 (m, 8H), 8.04 (s, 1H, 5-H), 8.45 (d, J=2.6 Hz, 1H); ^{13}C-NMR δ : 55.3 (q), 55.7 (q), 99.7 (d), 110.9 (d), 112.9 (s), 113.0 (d), 113.6 (s), 113.9 (d), 126.7 (s), 127.2 (d), 128.1 (d), 128.4 (d), 128.5 (d), 128.8 (d), 129.1 (s), 129.3 (d), 130.3 (s), 134.5 (s), 137.2 (s), 147.0 (s, CO), 149.7 (d, C=N), 159.0 (s), 163.4 (s); MS *m/z* 423 (M^+); IR(KBr) 1686, 1602 cm^{-1}. Anal. Calcd for $C_{26}H_{21}N_3O_3$: C, 73.74; H, 5.00; N, 9.92. Found: C, 73.91; H, 4.91; N,9.86.

*1,10-Dihydro-2,3-diphenyl-2H-imidazo[3,4-a]quinazolin-1-one (**3e**)*. Orange powder from EtOH ; mp 231-233 °C; ^{1}H-NMR δ: 6.80-7.80 (m, 13H), 8.14 (s, 1H, 5-H), 8.86 (d, J=8.4 Hz, 1H); ^{13}C-NMR δ : 116.0 (d), 119.7 (s), 124.8 (d), 127.4 (d), 127.5 (d), 127.6 (s), 128.1 (d), 128.2 (s), 128.8 (d), 128.9 (d), 133.2 (d), 134.7 (s), 135.4 (s), 147.1 (s, CO), 151.4 (d, C=N); MS *m/z* 337 (M^+); IR (KBr) 1698, 1590 cm^{-1}. Anal. Calcd for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46. Found: C, 78.23; H, 4.46; N, 12.22.

*3-Benzylidene-1,10-dihydro-2-phenyl-2H-imidazo[3,4-a]quinazolin-1-one (**3f**).* Red needles from EtOH; mp 213-215°C; ^{1}H-NMR δ: 6.89 (s, 2H), 7.15-7.70 (m, 14H), 8.15 (s, 1H, 5-H), 8.82 (d, J =8.4 Hz, 1H); ^{13}C-NMR δ: 112.8 (d), 113.6 (s), 116.1 (d), 120.0 (s), 125.1 (d), 126.1 (d), 127.4 (s), 127.5 (d), 128.2 (d), 128.5 (d), 128.6 (d), 129.4 (d), 133.3 (d), 134.4 (s), 135.4 (s), 137.3 (s), 147.2 (s, CO), 150.4 (d, C=N); MS *m/z* 363 (M^+); IR (KBr) 1694, 1524 cm^{-1}. Anal. Calcd for $C_{24}H_{17}N_3O$: C, 79.32; H, 4.71; N, 11.56. Found: C, 79.57; H, 4.58; N, 11.56.

*1,10-Dihydro-3-(4-methoxynaphthyl)-2-phenyl-2H-imidazo[3,4-a]quinazolin-1-one (**3g**).* Orange powder from EtOH; mp 218-220°C; ^{1}H-NMR δ: 3.99 (s, 3H), 6.77 (d, J = 7.5 Hz, 1H), 7.10-7.90 (m, 11H), 8.08 (s, 1H, 5-H), 8.10-8.35 (m, 1H), 8.96 (d, J =8.1 Hz, 1H); ^{13}C-NMR δ: 55.6 (q), 103.4 (d), 113.6 (s), 116.1 (d), 116.9 (s), 119.7 (s), 122.2 (d), 124.7 (d), 125.3 (d), 126.6 (d), 126.8 (s), 126.9 (d), 127.2 (d), 127.6 (d), 128.6 (d), 130.5 (d), 133.1 (d), 133.3 (s), 134.6 (s), 135.6 (d), 147.5 (s, CO), 151.1 (d, C=N), 156.3 (s); MS *m/z* 417 (M^+); IR (KBr) 1696, 1584 cm^{-1}. Anal. Calcd for $C_{27}H_{19}N_3O_2$: C, 77.68; H, 4.57; N, 10.07. Found: C, 77.91; H, 4.73; N, 9.96.

*4-Methoxy-2-(3-methyl-2,4-dioxo-4-phenylimidazolidin-1-yl)benzaldehyde (**4a**).* Colorless prisms from EtOH; mp 156-157°C; ^{1}H-NMR δ: 1.63 (d, J =7.7 Hz, 3H), 3.94 (s, 3H), 4.79 (q, J =7.7 Hz, 1H, CH), 6.94 (d, J =2.5 Hz, 1H), 7.12 (dd, J =8.0 and 2.5 Hz, 1H), 7.20-7.55 (m, 5H), 7.85 (d, J =8.0 Hz, 1H), 9.89 (s, 1H, CHO); ^{13}C-NMR δ: 15.5 (q), 56.0 (q), 56.8 (d), 114.9 (d), 116.3 (d), 122.3 (d), 125.3 (s), 125.7 (d), 129.2 (d), 132.6 (s), 135.5 (s), 136.2 (d), 156.2 (s, CO), 164.3 (s), 172.5 (s, CO), 188.4 (d, CO); MS *m/z* 324 (M^+); IR (KBr) 1776, 1712, 1675 cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.36; H, 4.78; N, 8.60.

*6-Methoxy-13-oxa-11,12-diphenyl-2-(piperidin-1-yl)-9,11,15-triazatetracyclo[7.6.0^{1,12}.0^{3,8}]pentadeca-3,5,7-triene-10,14-dione (**5b**).* Colorless needles from acetone; mp 203-205°C; ^{1}H-NMR δ: 1.25-1.60 (m, 6H), 2.10-2.42 (m, 4H), 3.80 (s, 1H, 2-H), 3.84 (s, 3H), 6.42 (br s, 1H, NH), 6.61 (dd, J =7.8 and 2.4 Hz, 1H), 6.93 (d, J =7.8 Hz, 1H), 7.10-7.63 (m, 6H); ^{13}C-NMR δ: 24.2 (t), 26.8 (t), 52.1 (t), 55.6 (q), 69.1 (d, C-2), 88.3 (s), 100.9 (s), 101.0 (d), 110.8 (d), 119.2 (s), 125.4 (d), 126.2 (d), 126.5 (d), 126.6 (d), 128.2 (s), 128.6 (d), 128.9 (d), 129.9 (d), 133.3 (s), 134.8 (s), 142.9 (s), 155.6 (s, CO), 161.0 (s); MS *m/z* 367 (M^+-$C_5H_{10}N$-CO_2); IR (KBr) 3345, 1794, 1709 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_4O_4$: C, 70.15; H, 5.68; N, 11.28.

Found: C, 69.99; H, 5.64; N, 10.98.

*13-Oxa-11,12-diphenyl-2-(piperidin-1-yl)-9,11,15-triazatetracyclo[7.6.0^{1,12}.0^{3,8}]pentadeca-3,5,7-triene-10,14-dione (**5e**).* Colorless plates from EtOH; mp 202-204°C; ^{1}H-NMR δ : 1.30-1.62 (m, 6H), 2.15-2.43 (m, 4H), 3.98 (s, 1H, 2-H), 6.60 (br s, 1H, NH), 6.90-7.79 (m, 14H); ^{13}C-NMR δ : 24.2 (t), 26.8 (t), 52.1 (t), 69.7 (d, C-2), 87.8 (s), 100.9 (s), 115.8 (d), 124.2 (d), 125.4 (d), 125.6 (d), 126.6 (d), 126.7 (d), 128. 1 (s), 128.2 (s), 128.6 (d), 129.0 (d), 129. 5(d), 130.0 (d), 133.3 (s), 134.9 (s), 141.2 (s), 155.6 (s, CO), 155.7 (s, CO); MS *m/z* 337 (M^+-$C_5H_{10}N$-CO_2); IR (KBr) 3415, 1782, 1730 cm^{-1}. Anal. Calcd for $C_{28}H_{28}N_4O_3$: C, 72.09; H, 5.62; N, 12.01. Found: C, 72.25; H, 5.57; N, 11.99.

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9. Detailed mechanism for the formation of **3** from **5** is equivocal at present. A reviewer has suggested a possibility that the decarboxylation from **5** should occur prior to the departure of piperidine.
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