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Syntheses of Di-heterocyclic Compounds; Pyrazolylimidazoles and Isoxazolylimidazoles

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ABSTRACT: *Fifteen substituted di-heterocyclic imidazoles were prepared. Ten substituted pyrazolylimidazoles were obtained by cyclocondensation of α-oxo-α-imidazolylketene dithioacetal or N,S-acetals with hydrazine and by ring-chain transformation of cyclic α-oxo-α-imidazolylketene N,O-acetals. Five isoxazolylimidazoles were obtained by reaction of α-oxo-α-imidazolylketene dithioacetal with hydroxylamine.*
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RESULTS AND DISCUSSION

Substituted di-heterocyclic compounds, such as pyrazolylimidazoles and isoxazolylimidazoles (Table 1) were obtained by three methods. First, substituted pyrazolylimidazole **2,** isoxazolylimidazole **3,** and **4** were synthesized by cyclocondensation of α-oxo-α-imidazolylketene dithioacetal **1** with bifunctional nucleophiles [1,2] such as hydrazine and hydroxylamine (Scheme 1).

Their structures were confirmed by spectroscopic data. The structures of **3** and **4** are isomers as determined by ^{1}H NMR and mass spectroscopy. In the high field of the proton spectrum, the protons of **4** resonate in a higher field than those of **3** because the inductive effect of O is a little stronger than that of N. For the same reason, in the low field of the proton spectrum, the protons of **4** resonate in a lower field than those of **3** (Table 2). The characteristic mass spectroscopy peaks of **3b** and **4b** are listed in Scheme 2.

Second, the ring-chain transformation of cyclic α-oxo-α-imidazolylketene N,O-acetals **5a–c** was investigated. The concept of ring-chain transformation is based on the opening of a saturated heterocyclic ring in the starting material while immediately afterward a new heteroaromatic ring is formed by condensation [3]. As starting intermediates, 1,3-dicarbonyl heteroanalogs were used. These substrates were "ring-chain" transformed by reaction with binucleophiles. We applied **5** as C–C–C building blocks and hydrazine as the binucleophile [4–7]. Pyrazolylimidazole compounds **6a–c** were obtained (Scheme 3).

Finally, we focused on the reaction of α-oxo-α-imidazole substituted acetophenones **7b–c** with phenyl isothiocyanate, followed by alkylation. α-Oxo-α-imidazolylketene N,S-acetals **8b–c** were obtained. On further reaction with hydrazine, new pyrazolylimidazole compounds **9b–c** were obtained (Scheme 4).

EXPERIMENTAL

Instruments

Melting points were determined with a Yanaco MP-500 apparatus without correction. ^{1}H NMR spectra were measured with a Jeol FX-90Q spectrometer using TMS as internal reference and mass spectra on a HP5988A spectrometer with 70 ev. Elemental analyses were performed on a MT-3CHN instrument.

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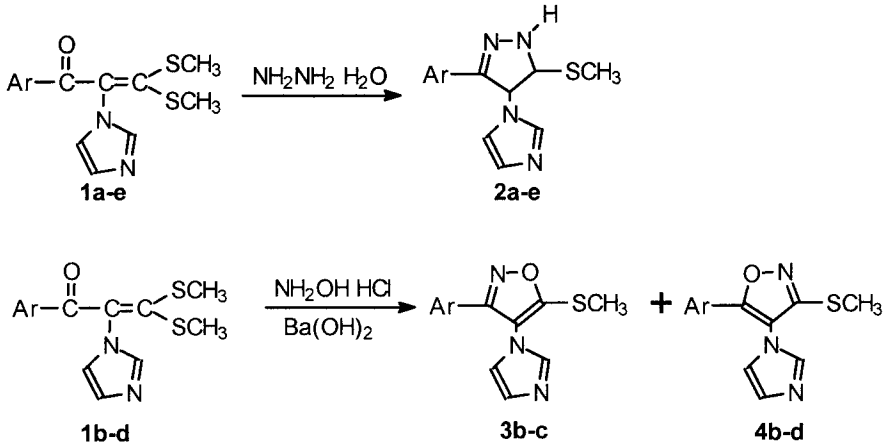
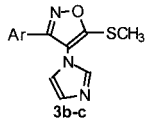
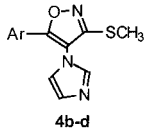


a, Ar = C_6H_5; **b,** Ar = p−ClC_6H_4; **c,** Ar = p−BrC_6H_4; **d,** Ar = p−$CH_3OC_6H_4$; **e,** Ar = p−$CH_3C_6H_4$.

SCHEME 1

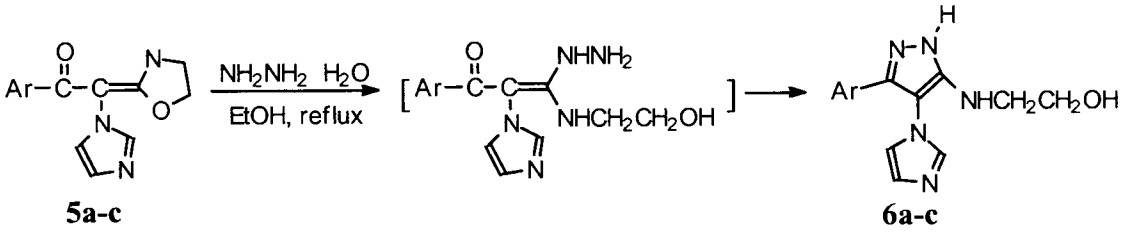


No.	Ar	Ar−C≡N^{+}	Ar−C=NH^{+}
3b	p−Cl C_6H_4	137	138
3c	p−BrC_6H_4	181	182



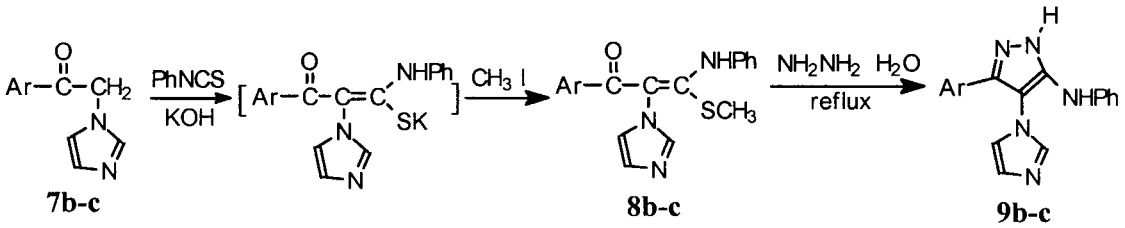
No.	Ar	Ar−C=O^{+}	Ar−C−OH^{+}
4b	p−Cl C_6H_4	139	140
4c	p−BrC_6H_4	183	/
4b	p−$CH_3OC_6H_4$	135	/

SCHEME 2



a, Ar = C_6H_5; **b,** Ar = p−ClC_6H_4; **c,** Ar = p−BrC_6H_4.

SCHEME 3



b, Ar = p−ClC_6H_4; **c,** Ar = p−BrC_6H_4.

SCHEME 4

TABLE 1 Preparation of Pyrazolylimidazoles and Isoxazolylimidazoles

No.	*Formula*	*Appearance*	*Mp* (°*C*)	*Yield* (%)	*Analysis* (%) *Calcd/Found* *C*	*H*	*N*
2a	$C_{13}H_{12}N_4S$	white needle	235.5–236.5	98	60.92/60.98	4.72/4.74	21.86/21.69
2b	$C_{13}H_{11}ClN_4S$	white needle	228.0–229.0	95	53.70/53.77	3.80/3.85	19.27/19.57
2c	$C_{13}H_{11}BrN_4S$	white needle	224.0–225.0	91	46.60/46.89	3.30/3.41	16.72/16.76
2d	$C_{14}H_{14}N_4OS$	white needle	196.0–198.0	90	58.71/59.14	4.93/5.17	19.56/20.00
2e	$C_{14}H_{14}N_4S$	white needle	206.5–207.5	90	62.22/61.95	5.22/5.30	20.72/20.48
3b	$C_{13}H_{10}ClN_3OS$	white needle	124.5–125.5	56	53.53/53.62	3.46/3.48	14.41/14.14
4b	$C_{13}H_{10}ClN_3OS$	yellow needle	178.0–179.0	22	53.53/53.22	3.46/3.58	14.41/14.23
3c/4c	$C_{13}H_{10}BrN_3OS$	yellow needle	157.0–158.5	40	46.44/46.39	3.00/2.96	12.50/12.50
4d	$C_{14}H_{13}N_3O_2S$	yellow needle	130.0–131.0	44	58.53/58.25	4.56/4.59	14.63/14.54
6a	$C_{14}H_{15}N_5O$	white needle	216.5–217.0	90	62.44/62.14	5.61/5.65	25.99/25.56
6b	$C_{14}H_{14}ClN_5O$	white needle	232.0–233.0	83	55.36/55.51	4.65/4.95	23.04/22.77
6c	$C_{14}H_{14}BrN_5O$	white needle	235.0–236.0	93	48.29/48.30	4.05/4.05	20.10/20.13
9b	$C_{18}H_{14}ClN_5$	white powder	272.0–273.0	70	64.38/64.48	4.20/4.51	20.85/20.77
9c	$C_{18}H_{14}BrN_5$	white powder	282.0–284.0	69	56.86/57.13	3.71/4.00	18.42/18.20

TABLE 2 ^{1}H NMR Data

No.	*^{1}H NMR, δ*
2a	(1) 2.40 (s, 3H, SCH_3), 7.16–7.60 (m, 8H, C_6H_5 & $C_3H_3N_2$), 13.68 (s, NH)
2b	(1) 2.38 (s, 3H, SCH_3), 7.16–7.66 (m, 7H, C_6H_4 & $C_3H_3N_2$), 13.80 (s, NH)
2c	(1) 2.36 (s, 3H, SCH_3), 7.12–7.56 (m, 7H, C_6H_4 & $C_3H_3N_2$), 13.72 (s, NH)
2d	(1) 2.40 (s, 3H, SCH_3), 3.76 (s, 3H, OCH_3), 6.88–7.68 (m, 7H, C_6H_4 & $C_3H_3N_2$), 13.58 (s, NH)
2e	(2) 2.32 (s, 3H, CH_3), 2.37 (s, 3H, OCH_3), 7.16–7.68 (m, 7H, C_6H_4 & $C_3H_3N_2$)
3b	(3) 2.62 (s, 3H, SCH_3), 6.95–7.54 (m, 7H, C_6H_4 & $C_3H_3N_2$)
4b	(3) 2.59 (s, 3H, SCH_3), 7.00–7.57 (m, 7H, C_6H_4 & $C_3H_3N_2$)
3c	(3) 2.60 (s, 3H, SCH_3), 6.93–7.52 (m, 7H, C_6H_4 & $C_3H_3N_2$)
4c	(3) 2.58 (s, 3H, SCH_3), 6.99–7.57 (m, 7H, C_6H_4 & $C_3H_3N_2$)
4d	(3) 2.68 (s, 3H, SCH_3), 3.80 (s, 3H, OCH_3), 6.90–8.01 (m, 7H, C_6H_4 & $C_3H_3N_2$)
6a	(1) 3.24 (t, 2H, NCH_2), 3.60 (t, 2H, OCH_2), 4.64 (s, OH), 7.20–7.50 (m, 8H, C_6H_5 & $C_3H_3N_2$), 8.12 [s, NH (branched)]
6b	(1) 3.20 (t, 2H, NCH_2), 3.60 (t, 2H, OCH_2), 4.60 (s, OH), 7.20–7.68 (m, 7H, C_6H_4 & $C_3H_3N_2$), 8.24 [s, NH (branched)]
6c	(1) 3.30 (t, 2H, NCH_2), 3.48 (t, 2H, OCH_2), 4.62 (s, OH), 7.10–7.63 (m, 7H, C_6H_4 & $C_3H_3N_2$), 7.50 [s, NH (branched)]
9b	(1) 6.50–8.00 [m, C_6H_4, $C_3H_3N_2$ & NH (branched)]. 13.00 [s, NH (pyrazole)]
9c	(1) 6.72–7.89 [m, C_6H_4, $C_3H_3N_2$ & NH (branched)], 13.06 [s, NH (pyrazole)]

(1) DMSO-d_6.
(2) CD_3OD.
(3) $CDCl_3$.

TABLE 3 EI-MS Data

No.	*m/z (abundant)*
2b	292 (39), 290 (M^+, 100), 264 (7), 262 (13), 248 (27), 250 (18), 179 (13), 140 (19), 138 (46), 113 (13), 111 (37), 102 (21)
3b	293 (4), 291 (M^+, 10), 246 (5), 244 (16), 218 (9), 216 (28), 140 (5), 139 (8), 138 (14), 137 (11), 113 (9), 111 (40), 102 (16), 79 (100)
4b	293 (42), 291 (M^+, 110), 246 (47), 244 (137), 142 (28), 141 (345), 140 (85), 139 (1000), 113 (156), 111 (522)
3c/4c	337 (47), 335 (M^+, 45), 290 (45), 288 (44), 262 (48), 260 (48), 242 (25), 240 (24), 228 (77), 201 (57), 199 (56), 185 (40), 184 (23), 183 (52), 182 (20), 181 (12), 157 (23), 155 (24), 111 (36), 79 (100), 52 (72)
4d	287 (M^+, 51), 272 (10), 240 (30), 135 (100), 111 (13), 92 (16), 79 (25)
6a	269 (M^+, 41), 238 (100), 211 (36), 104 (26), 77 (30)
6b	305 (15), 303 (M^+, 42), 274 (38), 272 (100), 247 (14), 245 (44), 140 (12), 138 (22), 113 (8), 111 (16)
6c	349 (45), 347 (M^+, 44), 318 (99), 316 (100), 291 (30), 289 (33), 237 (15), 184 (23), 182 (33), 157 (16), 155 (25), 76 (33), 75 (21)
9b	337 (37), 335 (M^+, 100), 309 (15), 307 (43), 140 (5), 138 (11), 113 (2), 111 (5), 77 (20)
9c	381 (95), 379 (M^+, 100), 353 (44), 351 (46), 184 (13), 182 (16), 157 (9), 155 (10), 93 (13), 91 (12)

General Procedure for the Preparation of **2a–c**

A mixture of **1** (2 mmol) and 85% hydrazine hydrate (360 mg, 6 mmol) in ethanol (20 mL) was refluxed for 2 hours. After evaporation of part of the solvent and cooling, precipitates formed that were collected and recrystallized from anhydrous ethanol.

General Procedure for the Preparation of **3b–c** *and* **4b–d**

Hydroxylamine hydrochloride (0.66 g, 9.3 mmol) was added to a stirred mixture of $Ba(OH)_2$ (4.7 mmol) in 20 mL of ethanol. Ten minutes later, **1** (3.1 mmol) was added, and then the mixture was heated at reflux for 0.5 hour. The solvent was evaporated under vacuum and the residue was diluted with water (40 mL). Acetic acid (36%) was added to the solution until pH = 5. Products were extracted by ethyl acetate (10 mL × 3) and dried with anhydrous sodium sulfate. The solvent was evaporated, and the products **3** and **4** were separated by column chromatography using petroleum ether/ethyl acetate as eluant.

General Procedure for the Preparation of **6a–c**

A mixture of **5** (0.78 mmol), 85% hydrazine hydrate (0.23 g, 3.9 mmol) and 20 mL of ethanol was refluxed for 4 hours. Part of the solvent was evaporated under vacuum. After cooling of the solution, the products **6** precipitated and were filtered off, then recrystallized from anhydrous ethanol.

General Procedure for the Preparation of **9b–c**

Phenyl isothiocyanate (1.2 mL, 10 mmol) and powdered KOH (0.8 g, 14 mmol) were added to a solution of **5** (10 mmol) in 20 mL of DMSO. The mixture was stirred at room temperature for 2 hours. Methyl iodide (1.4 g, 10 mmol) was gradually added over 4 hours. Addition of water (100 mL) caused a yellow precipitate **8b–c** to form. This was collected by filtration and then recrystallized from anhydrous ether.

Excess hydrazine hydrate (85%) was added to a mixture of **8** (3 mmol) and ethanol (40 mL). After the mixture had been refluxed for 3 hours, part of the solvent was evaporated under vacuum. The products **9b–c** were collected by filtration and recrystallized from DMF/H_2O.

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