One-Pot Synthesis of Spiro Pyrroloimidazoles and 2-Arylimidazoles from 1,2-Diaza-1,3-butadienes and Arylamidines

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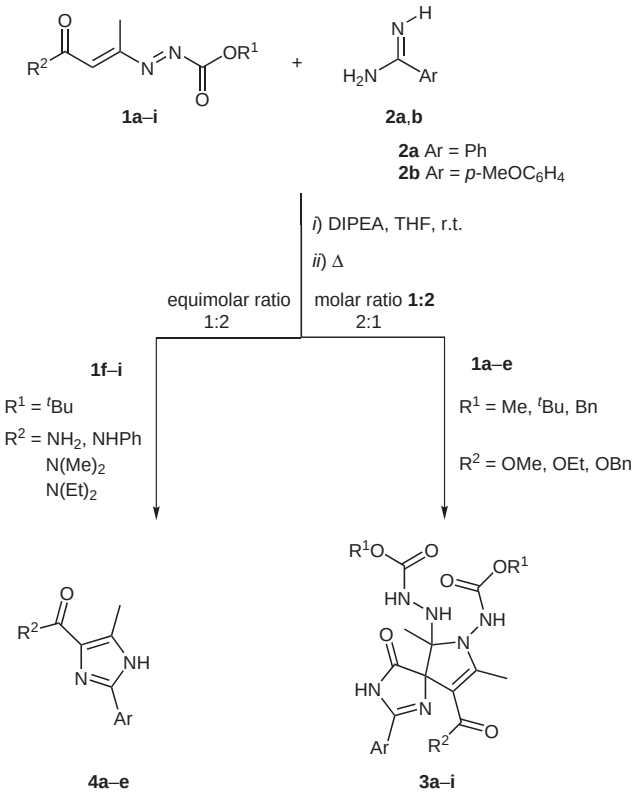
Abstract: 1,2-Diaza-1,3-butadienes react as Michael acceptors with nitrogen 1,3-dinucleophiles, such as arylamidines, in a one-pot heterocyclization reaction. Depending on the nature of the acyl residue at the terminal carbon of the heterodiene system, spiro pyrroloimidazole derivatives or 2-arylimidazoles can be obtained.

Key words: 1,2-diaza-1,3-butadienes, arylamidines, nucleophilic additions, cyclizations, spiro compounds

The electronic features of 1,2-diaza-1,3-butadienes[1] determine their great affinity to undergo regioselective nucleophilic attack at the terminal carbon of the azo–ene system (C4) by a variety of carbon- and heteronucleophiles affording 1,4-conjugate adducts.[2a] These acyclic intermediates bearing suitable nucleophilic and electrophilic functions can provide internal cyclization reactions that represents valuable methods for the construction of heterocyclic rings.[2b–g]

Indeed, considering 1,2-diaza-1,3-butadienes **1a**–**i** as Michael acceptors and arylamidines **2a**,**b** as 1,3-dinucleophile reagents, we explored their reactions to set up a strategy for the synthesis of compounds containing the imidazole[3] core since it occurs in a variety of alkaloids[4] and bioactive natural products[5] as well as in pharmaceutical agents.[6]

Initially, we investigated the reaction between 1,2-diaza-1,3-butadiene derivative **1a**, bearing an ester function at C4, and benzamidine (**2a**) in equimolar ratio in THF at room temperature. Despite the complete disappearance of **1a**, analysis of the crude mixture revealed unreacted benzamidine with a series of intermediates evolving during the time. The ^{1}H NMR spectrum of the main product formed allowed us to locate the presence in the compound of two units of 1,2-diaza-1,3-butadiene and one benzamidine fragment. This result suggested us that the amidine derivative worked as a nucleophile as well as a base. Therefore, we planned to carry out the reaction between **1a**–**e** and **2a**,**b** in a molar ratio of 2:1, respectively, using DIPEA (2 equiv) as base in THF at room temperature initially, then after the disappearance of the starting materials, under reflux (Scheme 1).



Scheme 1

This one-pot procedure[7] was able to afford directly the unknown spiro pyrroloimidazole derivatives **3a**–**i**[8] (52–78%, Scheme 1). A plausible mechanism of this spiroannulation reaction is presented in Scheme 2.

Similarly to our previous results,[9] the reaction proceeds via nucleophilic attack of arylamidine derivative **2** at C4 of the conjugated azoalkene system **1** to give hydrazone intermediate **A** by Michael-type addition. Subsequent ring closure at the ester function at C4 gives rise to 2-arylimidazolinone intermediate **B**. The base-promoted carbanion formation leads to nucleophilic 1,4-addition to another azoalkene molecule **1** affording compound **C**. Under basic conditions, the two hydrazone side chains of **C** co-operate

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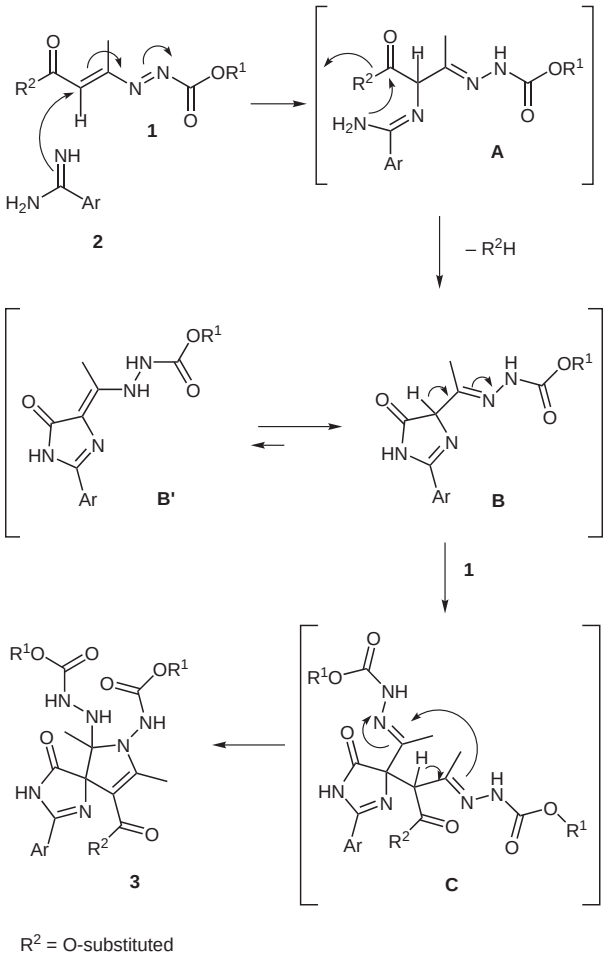

Scheme 2

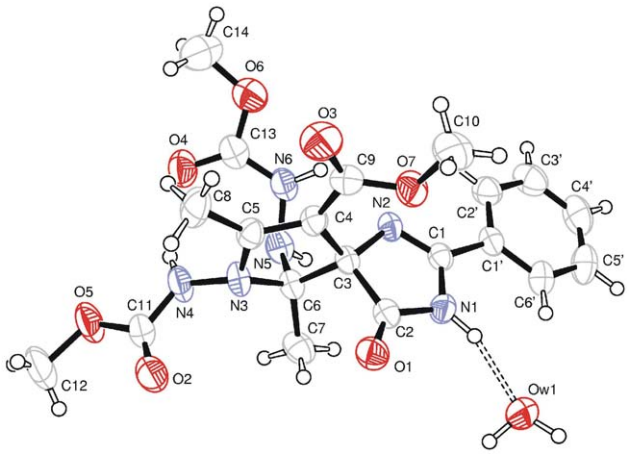

Figure 1 Drawing of the crystal structure of **3b**·H_2O

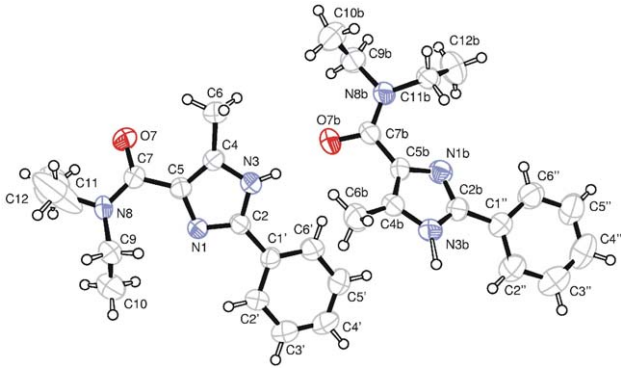

Figure 2 View of the asymmetric unit of **4c**

in the pyrrole ring closure producing spiro pyrroloimidazole derivative **3**. The hypothesized mechanism is supported by the occasional isolation of intermediate **B** in hydrazino tautomeric form **B′**[10] as a byproduct in the reaction between **1a** and **2a**. An X-ray diffraction study of one of the two diastereomers of **3b** confirmed the spiro heterobicyclic structure (Figure 1) and allowed the stereochemical assignment of the two stereogenic carbons to be established.[11]

Since the ester function at C4 of **1a**–**e** played a key role in the formation of **3a**–**i**, we proposed that its replacement with an amide residue would influence the outcome of the reaction. In fact, the reaction between **1f**–**i** and **2a**,**b** carried out in equimolar ratio and under same reaction conditions,[12] afforded new 2-arylimidazole derivatives **4a**–**e**[13] (52–78%, Scheme 1, Table 1). According to our previous findings,[2b,e] after preliminary conjugate addition, an intramolecular ring closure at the hydrazone function occurs producing a non-isolable 2-arylimidazoline intermediate because of its ready aromatization by loss of a hydrazine residue (Figure 2). The X-ray diffraction study of **4c** confirmed unequivocally the imidazole structure (Figure 2).[11]

In summary, herein we have reported the one-pot synthesis of novel spiro pyrroloimidazole derivatives under fast and mild reaction conditions, difficult to obtain by other procedures. Additionally, since 2-arylimidazoles[14] represent an important class of structures with antifungal,[15] NPY5 receptor antagonism[16] and macromolecular ligand properties,[17] the present study provides a new, simple one-pot entry to these compounds without any competitive arylpyrimidine formation.[14a]

Further investigations are currently in progress in order to improve and extend this strategy.

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Table 1 Results of the Synthesis of Spiro Pyrroloimidazoles **3a–i** and 2-Arylimidazoles **4a–e**

Entry	1,2-Diaza-1,3-butadiene **1**			Arylamidine **2**		Spiro pyrroloimidazoles **3**			2-Arylimidazoles **4**	
	1	R^1	R^2	**2**	Ar	**3**	Yield (%)[a] C5 (*R*/*S*), C6 (*S*/*R*)	Yield (%)[a] C5 (*R*/*S*), C6 (*R*/*S*)	**4**	Yield (%)[b]
1	**1a**	*t*-Bu	OMe	**2a**	Ph	**3a**	30	30		
2	**1b**	Me	OMe	**2a**	Ph	**3b**	36	26		
3	**1c**	*t*-Bu	OEt	**2a**	Ph	**3c**	27	27		
4	**1d**	Bn	OMe	**2a**	Ph	**3d**	30	22		
5	**1e**	*t*-Bu	OBn	**2a**	Ph	**3e**	26	26		
6	**1a**	*t*-Bu	OMe	**2b**	4-$MeOC_6H_4$	**3f**	38	31		
7	**1b**	Me	OMe	**2b**	4-$MeOC_6H_4$	**3g**	31	22		
8	**1d**	Bn	OMe	**2b**	4-$MeOC_6H_4$	**3h**	32	20		
9	**1e**	*t*-Bu	OBn	**2b**	4-$MeOC_6H_4$	**3i**	48	30		
10	**1f**	*t*-Bu	NH_2	**2a**	Ph				**4a**	76
11	**1g**	*t*-Bu	NMe_2	**2a**	Ph				**4b**	52
12	**1h**	*t*-Bu	NEt_2	**2a**	Ph				**4c**	71
13	**1i**	Me	NHPh	**2a**	Ph				**4d**	57
14	**1g**	*t*-Bu	NEt_2	**2b**	4-$MeOC_6H_4$				**4e**	78

[a] Yield of pure isolated diastereomer.
[b] Yield of pure isolated product.

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(7) **Procedure for the Preparation of Spiro Pyrroloimidazole Derivatives 3a–i**

1,2-Diaza-1,3-butadiene **1a–e** (2 mmol), prepared and used as a *EE*/*EZ*-isomer mixture,[1b] and DIPEA (2 mmol) were dissolved in THF (8 mL) under magnetic stirring. Then solid arylamidine **2a**,**b** (1 mmol) was added and the reaction mixture was allowed to stand at r.t. until complete disappearance of **1a–e** (0.25–1 h, monitored by silica gel TLC). The reaction mixture was then refluxed for the appropriate time (4–6 h). The solvent was removed under reduced pressure and the diastereomers of **3a–i** were obtained by silica gel chromatographic separation (eluent: CH_2Cl_2–EtOAc mixtures).

(8) **Data for Methyl 7-[(Methoxycarbonyl)amino]-6-[2-(methoxycarbonyl)hydrazino]-6,8-dimethyl-4-oxo-2-phenyl-1,3,7-triazaspiro[4.4]nona-1,8-diene-9-carboxylate (3b)**

5*R*/*S*,6*R*/*S*-Isomer

White powder from EtOAc–*n*-pentane, mp 161–163 °C (dec.). IR (Nujol): 3465, 3303, 3244, 3192, 1735, 1721, 1707, 1673, 1648, 1608, 1543, 1515 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.06 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 3.46 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 6.13 (s, 1 H, NH), 7.53 (t, *J* = 7.6 Hz, 2 H, Ar), 7.60 (t, *J* = 7.6 Hz, 1 H, Ar), 7.98 (d, *J* = 7.6 Hz, 2 H, Ar), 8.27 (s, 1 H, NH), 8.81 (s, 1 H, NH), 11.88 (s, 1 H, NH). ^{13}C NMR (100 MHz DMSO-d_6): δ = 11.58, 16.47, 50.31, 52.34, 81.45, 88.87, 96.90, 126.86, 128.37, 128.78, 131.82, 156.29,

156.95, 158.41, 163.86, 184.58. MS: *m*/*z* (%) = 460 [M^+] (4), 370 (100), 296 (22), 236 (42). Anal. Calcd for $C_{20}H_{24}N_6O_7$: C, 52.17; H, 5.25; N, 18.25. Found: C, 52.20; H, 5.22; N, 18.27.

5*R*/*S*,6*S*/*R*-Isomer

Colorless crystals from THF–*n*-pentane, mp 152–154 °C (dec.). IR (Nujol): 3484, 3435, 3339, 3306, 1744, 1723, 1687, 1620, 1602, 1578, 1511 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.15 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 3.42 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 5.90 (s, 1 H, NH), 7.56 (t, *J* = 7.6 Hz, 2 H, Ar), 7.62 (t, *J* = 7.6 Hz, 1 H, Ar), 7.90 (s, 1 H, NH), 8.04 (d, *J* = 7.6 Hz, 2 H, Ar), 8.64 (s, 1 H, NH), 11.65 (s, 1 H, NH). ^{13}C NMR (100 MHz DMSO-d_6): δ = 11.86, 17.06, 50.31, 52.31, 52.46, 80.22, 85.91, 96.72, 127.37, 128.35, 128.75, 132.18, 156.46, 156.54, 161.88, 163.64, 164.18, 183.08. MS: *m*/*z* (%) = 460 [M^+] (1), 370 (100), 296 (21), 236 (18). Anal. Calcd for $C_{20}H_{24}N_6O_7$: C, 52.17; H, 5.25; N, 18.25. Found: C, 52.16; H, 5.23; N, 18.26.

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(10) Data of **B'**: ^1H NMR (400 MHz, DMSO-d_6): δ = 1.39 (s, 9 H, O*t*-Bu), 1.94 (s, 3 H, CH_3), 6.86 (s, 1 H, NH), 7.54 (t, *J* = 7.6 Hz, 2 H, Ar), 7.61 (t, *J* = 7.6 Hz, 1 H, Ar), 7.95 (d, *J* = 7.6 Hz, 2 H, Ar), 9.64 (s, 1 H, NH), 11.41 (s, 1 H, NH). ^{13}C NMR (100 MHz DMSO-d_6): δ = 11.99, 27.97, 79.19, 93.64, 127.09, 128.38, 128.76, 132.26, 151.66, 152.66, 160.86, 181.69. MS: *m*/*z* (%) = 317 [M^+ + 1] (0.5), 260 (3), 216 (12), 202 (57), 104 (100).

(11) Crystallographic data (excluding structure factors) for compound **3b** and **4c** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 637246 and 637245. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

(12) **Procedure for the Preparation 2-Arylimidazole Derivatives 4a–e**

To a solution of 1,2-diaza-1,3-butadiene **1f**–**i** (1 mmol) and DIEA (1.2 mmol) in THF (6 mL) solid arylamidine **2a**,**b** (1 mmol) was added under magnetic stirring at r.t. After the disappearance of **1f**–**i** (0.25–0.5 h) the reaction mixture was refluxed (4–6 h). Compound **4a** was obtained by direct crystallization from the reaction medium and was filtered off with satisfactory purity whereas compounds **4b**–**e** were obtained after chromatographic purification (elution: CH_2Cl_2–EtOAc mixtures).

(13) **Data for *N*,*N*-Diethyl-5-methyl-2-phenyl-1*H*-imidazole-4-carboxamide (4c)**

Colorless crystals from Et_2O, mp 187–190 °C. IR (Nujol): 3114, 1595,1566, 1538, 1494 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.14 (br s, 3 H, CH_3), 1.23 (br s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 3.37 (br s, 2 H, NCH_2), 3.77 (br s, 2 H, NCH_2), 7.34 (t, *J* = 7.6 Hz, 1 H, Ar), 7.45 (t, *J* = 7.6 Hz, 2 H, Ar), 7.90 (d, *J* = 7.6 Hz, 2 H, Ar), 12.59 (s, 1 H, NH). ^{13}C NMR (100 MHz DMSO-d_6): δ = 10.84, 12.97, 14.68, 39.66, 42.45, 124.59, 128.01, 128.70, 130.33, 132.54, 132.76, 142.21, 164.12. MS: *m*/*z* (%) = 257 [M^+] (27), 185 (100), 158 (99). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.99; H, 7.47; N, 16.35.

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