Synthesis of Novel Spiro Cyclic 2-Oxindole Derivatives of 6-Amino-4*H*-Pyridazine via [3+3] Atom Combination Utilizing Chitosan as a Catalyst

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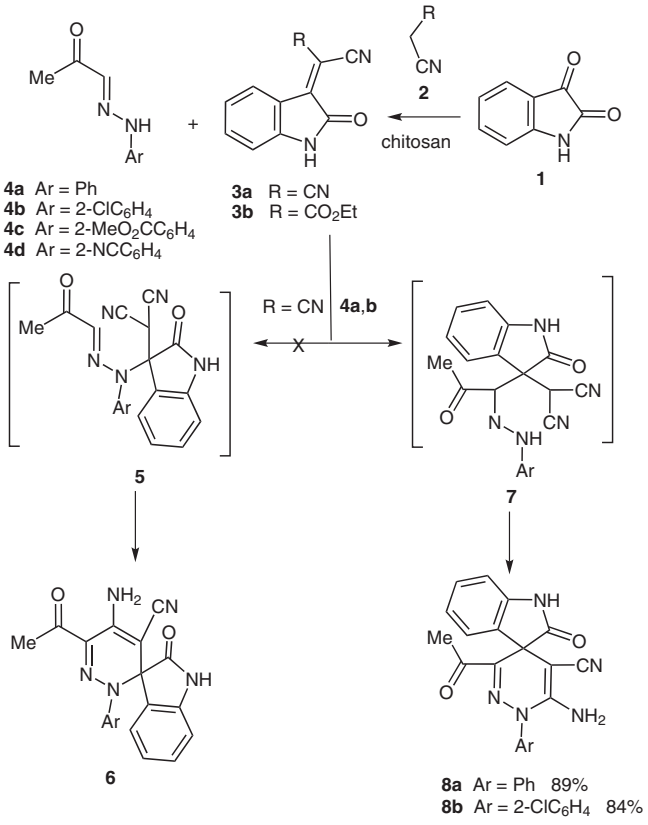
Abstract: Azaenamines were reacted with 3-cyanomethylidene-2-oxindoles using chitosan catalyst to yield spirocyclic 2-oxindole derivatives of 6-amino-4*H*-pyridazine and fused pyridazinoquinazolines.

Key words: aza-enamine, chitosan, Michael addition, 3-spiro-pyridazines-2-oxindoles

The heterocyclic spirooxindole ring system is a widely distributed structural framework present in a number of pharmaceuticals and natural products,[1,2] The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets.[3–6] Azaspiro derivatives are well known,[3–8] but the preparation of the corresponding oxa analogues has evolved at a relatively slow pace.[9]

In conjunction to our interest in developing syntheses for biologically interesting pyridazines,[10–12] the possibility of [3+3] atom combination of pyruvaldehyde-1-arylhydrazones **4a–d** with 3-cyanomethylidene-2-oxindoles **3a**,**b** through Michael addition reaction was studied. Compound **3** was prepared by reacting isatin **1** with **2** in the presence of chitosan as a catalyst (as shown in Scheme 1) or in the presence of triethyamine as described in the literature.[13] Chitosan, which is an amino polysaccharide, was also used as a substitute to the carcinogenic piperidine and pyridine catalysts and the yield (%) was found to be higher in the case of chitosan (cf. Table 1). Compounds **4a**,**b** reacted with compound **3a** in the presence of chitosan to yield spiropyridazines that may be formulated as **6** or **8**.[14] If the initial addition involves the NH of aza-enamine to the activated double bond in **3a**, Michael adduct **6** would be formed. On the other hand, if the initial addition involves the hydrazone CH to the activated double bond in **3a**, Michael adduct **8** would be formed. The NOE difference experiment revealed enhancement of aryl protons on irradiating the NH_2 group at $\delta = 6.14$ ppm, and this is in agreement with structure **8** (cf. Scheme 1).[15] The structure of compounds **8** was also simply elucidated chemically by reacting pyruvaldehyde-1-arylhydrazones **4c**,**d** (carrying substituent on *ortho* position) with 3-cyanomethylidene-2-oxindoles **3**, where only further cyclization occurred in the case of 6-aminopyridazines, while in the case of 4-aminopyridazines no further cyclization occurred. Thus the reaction of **4c** with **3a** results in the formation of product of cyclization with methanol elimination to give compound **9**.[16] The formation of **9** rather than **8** also excludes the initial addition of NH to the double bond in **2** to give **6**. The structure of compound **9** was confirmed based on MS and NMR spectra that revealed the absence of the OMe group.[17] Also reacting **4d** with **3a** has resulted in the formation of a product that can be formulated as **10**. It is believed that initially **8** is formed and cyclized into **10** (cf. Scheme 2).



Scheme 1

On the other hand, it was found that heating 3-cyano methylidene-2-oxindole (**3b**) with pyruvaldehyde-1-arylhydrazone (**4a**) in ethanol–piperidine solution resulted in the formation of a mixture of **12** and another product **13**

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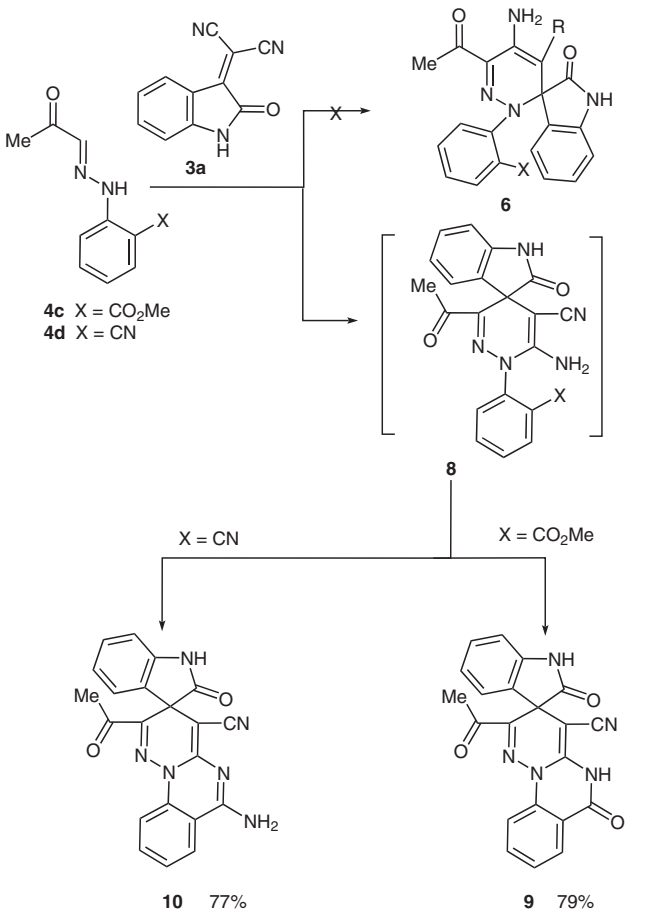
Table 1 Synthesis of Compounds **8**–**10** and **12** Using Different Catalysts

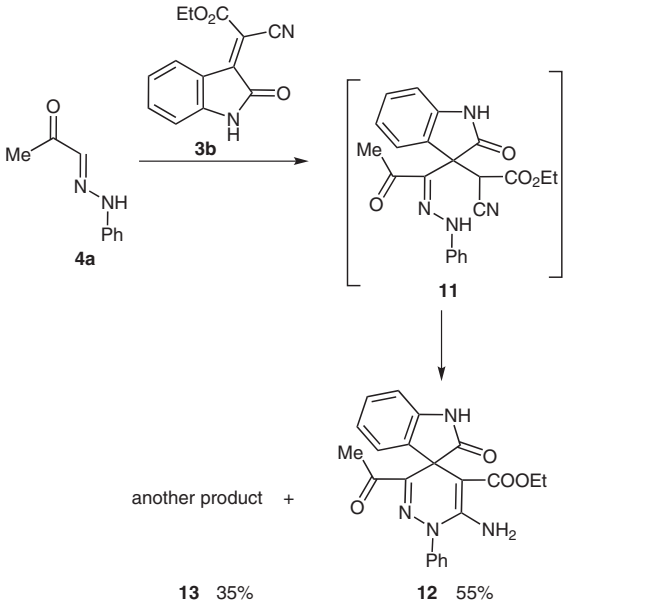
Compound	Yield (%)	
	Using piperidine	Using chitosan
8a	78	89
8b	76	84
9	74	79
10	75	77
12	52	55



Scheme 2

that results most likely via addition of **3b** to **4a** followed by elimination of water. Spectral data of compound **12** are in complete agreement with the proposed structures (cf. Scheme 3)[18] while the structure of the side product **13** is still under investigation.[19]

Finally, the regioselectivity of the addition can be easily explained on the basis that the delocalization of the nitrogen lone pair make hydrazone CH more nucleophlilic than NH (as shown in Figure 1), so the hydrazone CH adds first on the activated double bond in **3** to give the acyclic intermediate **7** that readily cyclizes into Michael adduct **8**.



Scheme 3

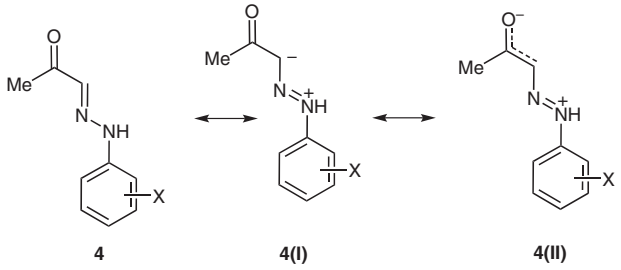


Figure 1

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(14) **General Procedures for Compounds 8a,b and 12**
Method A: A mixture of aza-enamine **4** (10 mmol) and 3-cyanomethylidene-2-oxindoles **3** was refluxed in EtOH (20 mL) in the presence of piperidine (0.1 mL) for 3 h. The solvent was evaporated under vacuum, and the crude product was collected and crystallized from EtOH or EtOH–dioxane.
Method B: A mixture of arylhydrazone **4** (10 mmol) and 3-cyanomethylidene-2-oxindoles **3** was refluxed in EtOH (20 mL) in the presence of chitosan (0.2 g) for 3 h. The solvent was evaporated under vacuum, and the crude product was collected and crystallized from EtOH or EtOH–dioxane. The catalyst chitosan was removed by filtration prior or during the crystallization process.
(15) **4,3′-Spiro(3-acetyl-6-amino-1-phenyl-1*H*,4*H*-pyridazine-5-carbonitrile)-2′-oxindole (8a)**
Mp 262–264 °C. IR (KBr): ν = 3444, 3359, 3220 (NH_2 and NH), 2190 (CN), 1724, 1623 (2 CO) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.18 (s, 3 H, CH_3-CO), 6.14 (br s, 2 H, NH_2), 6.83–7.58 (m, 9 H, Ar H), 10.57 (br s, 1 H, indole NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.7 (CH_3), 48.5 (spiro C), 59.7 (CCN), 109.5, 118.0 (CN), 122.1, 123.8, 126.6, 128.7, 129, 129.7, 134.4, 139.9, 140.6 (Ar CH), 141.3 ($CCOCH_3$), 149.7 (CNH_2), 177 (CONH), 194.8 (CO). MS (EI): *m/z* (%) = 357 [M^+].
(16) **General Method for the Synthesis of Compounds 9 and 10**
A solution of each of **4c** or **4d** (10 mmol) was treated with compound **3a** (10 mmol) in pyridine (10 mL). The solution was refluxed for 5 h, then poured onto H_2O and acidified with dilute HCl. The solid product obtained was crystallized from EtOH or EtOH–dioxane.
(17) **4,3′-Spiro{2-acetyl-6-oxo-3-phenyl-3,5,6,11-tetrahydropyridazino[1,6-*a*]quinazoline-4-carbonitrile}-2′-oxindole (9)**
Mp >300 °C. IR (KBr): ν = 3376, 3189 (2 NH), 2196 (CN), 1735, 1693, 1633 (3CO) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.46 (s, 3 H, CH_3CO), 6.86–8.00 (m, 8 H, Ar H), 10.78 (br s, 1 H, indole NH), 11.79 (br s, 1 H, pyrimidine NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.5 (CH_3), 49.6 (spiro C), 66.4 (CCN), 109.7, 114.4, 114.9, 115.7 (CN), 122.3, 124.8, 126.8, 127.3, 129.9, 133.5, 139.7, 141.2, 142,5, (Ar CH), 141.3 ($CCOCH_3$), 149.7 (CNH_2), 162, 176.2 (2 CONH), 194.0 (CO). MS (EI): *m/z* (%) = 383 [M^+].
(18) **4,3′-Spiro(ethyl 3-acetyl-6-amino-1-phenyl-1*H*,4*H*-pyridazine-5-carboxylate)-2′-oxindole (12)**
Mp 244–246 °C. IR (KBr): ν = 3496, 3428, 3237 (NH_2 and NH), 1720, 1644, 1608 (3 CO) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 0.87 (t, 3 H, CH_3, *J* = 7.2 Hz), 2.11 (s, 3 H, CH_3CO), 4.2 (q, 2 H, CH_2, *J* = 7.2 Hz), 6.71 (br s, 2 H, NH_2), 6.86–7.89 (m, 9 H, Ar H), 10.31 (br s, 1 H, indole NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.2 (CH_3), 25.4 (CH_3), 48.6 (CH_2), 56.9 (spiro C), 76.5 (CCN), 108.5, 119.3, 126.9, 128.7, 129.9, 132.8, 136,9, 141.1, 142.9, 143.1 (Ar CH), 144.5 ($CCOCH_3$), 149.4 (CNH_2), 167.9 (CONH), 179.1 (CO_2Et), 194.8 (CO). MS (EI): *m/z* (%) = 404 [M^+].
(19) **Spectral Data of Compound 13**
Mp 285 –287 °C. IR (KBr): ν = 3120, 3245, 1646 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 1.21 (t, 3 H, CH_3, *J* = 7.2 Hz), 2.62 (s, 3 H, CH_3CO), 4.25 (q, 2 H, CH_2, *J* = 7.2 Hz) 6.84–7.84 (m, 9 H, Ar H), 9.00 (s, 1 H), 13.40 (br s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.1, 15.5, 63.8, 73, 116.8, 118.6, 119.6, 120.9, 121, 123.3, 123.9, 124.5, 125.5, 128.1, 128.8, 136.3, 139.8, 145.6, 155.7, 165.8. MS (EI): *m/z* (%) = 386 [M^+].