A Novel and Practical Amination of 4,5-Dichloropyridazin-3-ones via Reduction with Hydrazine Hydrate

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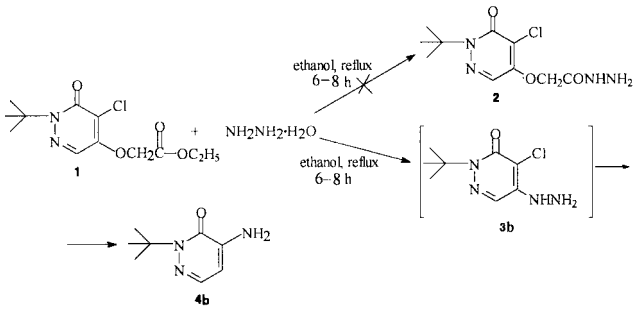
(Received September 14, 2000; CL-000855)

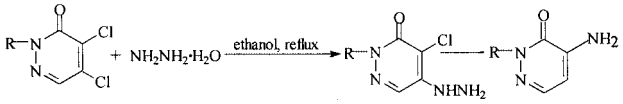
A novel and simple protocol: the direct amination of 4,5-dichloropyridazinones can be carried out in hydrazine hydrate under mild conditions. 4-Chloro-5-hydrazinopyridazin-3-ones serves as a key intermediate in this reduction.

It is known that hydrazine hydrate is a reducing agent which can reduce aldehydes and ketones to hydrocarbon requiring relatively harsh conditions,[1] aromatic nitro compounds to aromatic amines[2] and alkyl halides to corresponding alkanes in the presence of metal catalyst, respectively.[2,3] In this communication, we like to report a novel and efficient synthesis of 2-(un)substituted-4-aminopyridazin-3-ones by reduction of 2-(un)substituted-4,5-dichloropyridazin-3-ones under mild conditions with hydrazine hydrate. During the course of our studies on pyridrazinones, treatment of 2-*tert*-butyl-4-chloro-5-(ethoxycarbonylmethoxy)-3(2*H*)-pyridazin-3-one **1** with hydrazine hydrate in ethanol under the conditions indicated in Scheme 1, afforded an unexpected product **4b** with good yield, whereas the anticipated compound namely acetylhydrazine **2**, was not obtained. This reaction is very unusual. Alazawe reported that methoxy at 6-position of the pyridazinone can be replaced by the hydrazino group.[4] From this point, we assumed that the first step of this reaction was the formation of intermediate **3b**.



Scheme 1.

Aminopyridazinones have been shown to be useful intermediates for the access to amino agricultural chemicals and pharmaceutical products. General methods lead to amino pyridazinone involving Raney-Ni cleavage of the hydrazino pyridazinone,[5] the direct amination of the pyridazinones[6–8] and the substitution of chloropyridazinone with ammonia at enhanced pressure, [9] but they were much different from the reaction we metioned above. On the other hand, the dechlorination of chloropyridazinone should be performed in the presence of palladium on charcoal.[8] To explore this somewhat unusual reaction, we designed the following synthetic Scheme 2. 2-(Un)substituted-4,5-dichloropyridazin-3-ones **2a-c** gave 2-(un)substituted-4-aminopyridazin-3-ones **4a-c** when allowed to react with



2a-c **3a-c** **4a-c**
a R= H **b** R= t-butyl **c** R= phenyl

Scheme 2.

hydrazine hydrate in ethanol under reflux 6–8 h.

From the literature, conversion of **2a, 2c** into **3a, 3c** was accomplished efficiently[5,10] when refluxed in ethanol with hydrazine for short periods of time (1–2 h). Following the above procedures, reaction of **2b** with hydrazine hydrate under reflux for 1 h, monitoring the course of the reaction on TLC, gave just a major product which was identified as 2-*tert*-butyl-4-chloro-5-hydrazinopyridazin-3-one **3b**. Prolonged reaction time (8 h), or further reaction of the crude product with fresh hydrazine hydrate, gave complete conversion of **2b** to **4b**. The similar products were observed in the reaction of **2a, 2c** with hydrazine in different reaction stage. Those results confirmed the assumption that **3a-c** is an intermediate in the reaction of **2a-c** with hydrazine hydrate. The yields, reaction conditions, substrates and products of **2** → **3**, **3** → **4**, **2** → **4** were listed on Table 1.[12,13]

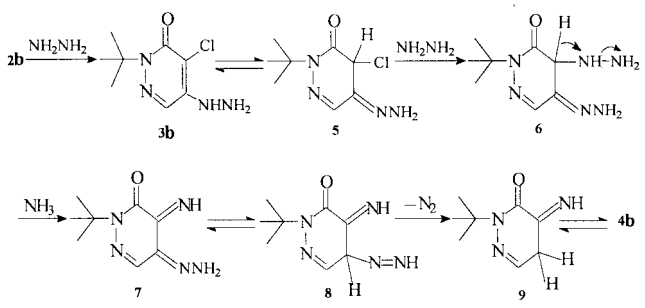
Table 1. The yields, reaction conditions, substrates and products of 2 → 3, 3 → 4, 2 → 4

Substrate	Product	Temp./°C	Time /h	Yield /%
2a	**3a**	70*	1.5	69[5]
2b	**3b**	70*	1	76
2c	**3c**	70*	2	75[5]
3a	**4a**	85	5	88
3b	**4b**	85	5	89
3c	**4c**	85	6	85
2a	**4a**	85	8	65
2b	**4b**	85	6	70
2c	**4c**	85	8	62

* methanol as solvent

In order to explain the formation of **4a-c**,[14] we suggested the following mechanism Scheme 3. **3b** can be written as **5** and undergo another hydrazine incorporation in exchange for Cl-4 to form **6**. This intermediate, in turn, may loose NH_3 to form **7** and tautomerize to **8** which then further looses dinitrogen. The product **9** of this homolytic fragmentation would then be just a tautomer of **4b**. Harsh conditions may probably not be needed since carbons 3,4,5 constitute also a 1,3-dicarbonyl system and C-5 is doubly activated.

The position of amino was identified on the basis of coupling constants of the ^{1}H NMR spectrum of **4a-c**. The coupling constant of **4a** was in complete agreement with the literature value for the 4-aminopyridazin-3-one ortho coupling constant,[8] whereas the meta coupling constant of pyridazinone is small (J = 3.0 Hz).[11] The coupling constants of **4b, 4c** were analogous to that of **4a** (J = 4.7 Hz). Homonuclear (^{1}H–^{1}H) correlation further confirmed the conclusions drawn from the ^{1}H NMR, and clearly showed the interaction within two ortho protons. The determination of the position of amino should be helpful to understand the mechanism of the reduction reaction.



Scheme 3.

The influence of polar solvents on the yield of the reduction reactions was also observed. When we used benzene instead of ethanol as the solvent, the yield of **4b** reduced to 40%. Furthermore **4b** was formed in only 20% yield by using anhydrous hydrazine in anhydrous benzene. Those results showed that polar solvents are favourable to the reaction.

In conclusion, a novel and convenient route has been developed. Thus this method provides a simple, operationally easy way for the preparation of these useful intermediates, which are of potential importance in the pharmaceutical industry and are not easily accessible by previous methods. Studies are underway to extend the reaction to other heterocycles, as well as to study in detail the mechanistic features of the new method.

References and Notes

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12 Typical procedure for aminopyidazinones **4**: A stirred mixture of the dichloropyridazinone **2** (2.26 mmol), hydrazine hydrate (22.6 mmol) and ethanol (15 mL) was heated at 85 °C for 8 h, then concentrated to dryness in vacuo and separated by chromatography using silica gel with petroleum ether/ethyl acetate (4/1). (**4a** was purified by recrystallization in H_2O).
13 Selected data for **3b**: Yield 75%, mp 133–134 °C; IR (cm^{-1}) 3380, 3328, 3170, 1640, 1610, 1420, 1360; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58 (9H, s, $(CH_3)_3C$), 5.76 (2H, br, NH_2), 6.68(1H, br, s, NH), 8.17(1H, s, H-6); ^{13}C NMR(125 MHz, $CDCl_3$): δ 28.8(C-2'), 66.1(C-1'), 107.2(C-4), 125.9(C-5), 146.1(C-6), 158.8(C-3); EI-MS(70eV): *m/z*(%): 216(5), 160(52), 125(25), 97(48), 56(74), 41(100), 29(84); Anal. Found: C, 44.24; H, 6.15; N, 26.17%. Calcd for $C_8H_{13}ClN_4O$: C, 44.33; H, 6.05; N, 25.85%. Selected data for **4b**: Yield 70%, mp 109–110 °C; IR (cm^{-1}) 3480, 3400, 3340, 1640, 1600, 1540, 1360; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.69 (9H, s, $(CH_3)_3C$), 5.29 (2H, br, NH_2), 6.33(1H, d, J = 4.7 Hz, H-5), 7.59(1H, d, J = 4.7 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.4(C-2'), 65.0(C-1'), 101.6(C-5), 136.7(C-4), 145.4(C-6), 157.7(C-3); EI-MS(70eV): *m/z*(%): 167(62), 111(100), 83(30), 57(20), 55(35), 41(47); Anal. Found: C, 57.42; H, 7.93; N, 25.30%. Calcd for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13%.
14 According to reference 8, **4a** was synthesized by the reaction of 4-amino-6-chloro-3(2*H*)-pyridazinone, sodium hydroxide with 10% Pd-C and water, shaked under hydrogen at atmospheric pressure, the data of ^{1}H NMR is as follow: 6.18(d, J = 4.7 Hz, 1H, H-5); 6.33(br s, 2H, NH_2); 7.47(d, J = 4.7 Hz, 1H, H-6); 12.50(br s, 1H, H-2). The data of ^{1}H NMR of **4a** which was synthesized by our method IS as follows: 6.17(d, J = 4.7 Hz, 1H, H-5); 6.28(br s, 2H, NH_2); 7.46(d, J = 4.7 Hz, 1H, H-6); 12.50(br s, 1H, H-2).