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N-Nitration of Secondary Amines with 4-Chloro-5-methoxy-2-nitropyridazin-3-one

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Abstract: *N*-Nitration of 4-chloro-5-substituted-pyridazin-3-one with copper nitrate trihydrate in acetic anhydride gave the corresponding 4-chloro-2-nitro-5-substituted-pyridazin-3-one. 4-Chloro-5-alkoxy-2-nitropyridazin-3-ones such as 5-methoxy (**2b**) and 5-ethoxy (**2d**) derivatives showed excellent nitro group transfer potentiality. *N*-Nitration of some secondary amines with **2b** gave the corresponding *N*-nitramines under mild neutral condition in good yields.

Many *N*-nitramines have been produced over the years because of their importance as energetic materials[1] and biologically active nucleosides.[2]

The most common method of preparing *N*-nitramines is by direct nitration of amino derivatives with acetone cyanohydrin nitrate,[3] $CF_3CMe_2ONO_2$,[4] N_2O_5,[1i,5] HNO_3,[1j,6] or NH_4NO_3[7] in trifluoroacetic anhydride and $NO_2OSO_2CF_3$.[8] Also Daszkiewicz et al.[9] reported on the conversion of secondary arylamines into corresponding nitramines by acting *n*-butyl nitrate with organomagnesium bromide. These methods suffer the inconvenience of handling, low yield, or potential explosion hazard because of the requirements of special preparation.[10] Thus, we were interested in finding a mild and stable reagent for the *N*-nitration of secondary amines. As we continued our research on the synthesis and the application of 2-substituted pyridazin-3-ones containing a useful functional group at the 2-position on the pyridazin-3-one ring,[11] we found that 2-acyl or 2-benzenesulfonyl-4,5-dichloropyridazin-3-ones serve as excellent *N*-acylating or *N*-benzenesulfonylating reagents for amines under neutral conditions. 4,5-Dichloropyridazin-3-one also is a good leaving group. Thus, we have investigated the synthesis and *N*-nitro transfer potentiality of 2-nitropyridazin-3-ones to secondary amines. This paper reports on a simple and convenient method using a new reagent for effective *N*-nitration of secondary amines (**3**) to their corresponding *N*-nitro derivatives (**4**) under mild conditions.

TABLE 1. 2-Nitropyridazin-3-ones Prepared

entry	substrate	conditions[a]	yield[b] of **2** (%)
1	**1a**	$Cu(NO_3)_2{\cdot}3H_2O$, Ac_2O, rt, 2 h	**2a** (90)
2	**1a**	NH_4NO_3, $(CF_3CO)_2O$, CH_2Cl_2, rt, 2 h	**2a** (80)
3	**1a**	TBAN, $(CF_3CO)_2O$, CH_2Cl_2, 0 °C, 3 h	**2a** (60)
4	**1a**	concd H_2SO_4, concd HNO_3	**2a** (0)
5	**1b**[11d]	$Cu(NO_3)_2{\cdot}3H_2O$, Ac_2O, rt, 1.5 h	**2b** (85)
6	**1c**[11d]	$Cu(NO_3)_2{\cdot}3H_2O$, Ac_2O, rt, 1 h	**2c** (81)
7	**1d**[11d]	$Cu(NO_3)_2{\cdot}3H_2O$, Ac_2O, rt, 1.5 h	**2d** (80)
8	**1e**[11d]	$Cu(NO_3)_2{\cdot}3H_2O$, Ac_2O, rt, 2 h	**2e** (85)
9	**1f**	$Cu(NO_3)_2{\cdot}3H_2O$, Ac_2O, rt, 2 h	**2f** (88)

[a] rt = room temperature. TBAN = tetrabutylammonium nitrate. [b] Isolated yield.

Direct *N*-nitration of 4,5-dichloropyridazin-3-one (**1a**) was performed with some nitrating reagents such as $Cu(NO_3)_2/Ac_2O$, $NH_4NO_3/(CF_3CO)_2O$ in methylene chloride, tetrabutylammonium nitrate/$(CF_3CO)_2O$ in methylene chloride, and concd H_2SO_4/concd HNO_3 (Table 1). Our experimental results demonstrated that $Cu(NO_3)_2$ is the best reagent for *N*-nitration of **1a** to **2a**. Thus, *N*-nitration of some pyridazin-3-ones **1b**−**f** with $Cu(NO_3)_2$ in acetic anhydride at room temperature afforded the corresponding *N*-nitro derivatives **2b**−**f** in good yields.

To evaluate their *N*-nitro transfer potentiality, *N*-nitration of *N*-methylbenzylamine (**3a**) as a secondary amine with **2a**−**f** was conducted in dichloromethane at room temperature. The results are shown in Table 2 (entries 1−6). Among six *N*-nitropyridazin-3-ones, 5-alkoxy

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SCHEME 1

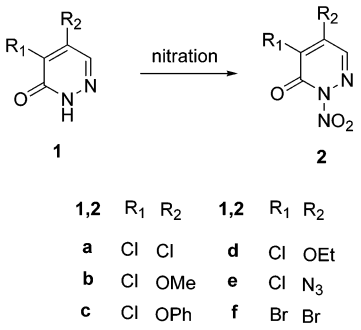


TABLE 2. ***N*-Nitration of *N*-Methylbenzylamine with 2-Nitro-pyridazin-3-ones 2a−c, 2e, and 2g**

entry	**2**	conditions[a]	yield[b] of **4a** (%)
1	**2a**	CH_2Cl_2, rt, 4 h	trace[c]
2	**2b**	CH_2Cl_2, rt, 1 h	95
3	**2c**	CH_2Cl_2, rt, 0.5 h	18[c]
4	**2d**	CH_2Cl_2, rt, 2.5 h	92
5	**2e**	CH_2Cl_2, rt, 3 h	44[c]
6	**2f**	CH_2Cl_2, rt, 5 h	10[c]
7	**2b**	*n*-hexane, rt, 5 h	70
8	**2b**	AcOEt, rt, 1 h	90
9	**2b**	THF, rt, 8 h	84
10	**2b**	Et_2O, rt, 2 h	87
11	**2b**	MeOH, rt, 10 h	55
12	**2b**	CH_3CN, rt, 1 h	88

[a] rt = room temperature. [b] Isolated yield. 4-Chloro-5-methoxypyridazin-3-one was also recovered in good yield in entries 2, 7, and 9. [c] Several unknown products were also detected on TLC.

TABLE 3. ***N*-Nitration of Some Secondary Amines 3 with 2b in CH_2Cl_2 at Room Temperature**

entry	secondary amine **3**	time (h)	yield[a] of **4** (%)
1	*N*-isopropylbenzylamine (**3b**)	8	**4b** (86)
2	diethylamine (**3c**)	1	**4c** (90)
3	dicyclohexylamine (**3d**)[b]	49	**4d** (28)
4	morpholine (**3e**)	2.5	**4e** (92)
5	2,6-dimethylmorpholine (**3f**)	3	**4f** (74)
6	3-pyrroline (**3g**)	3	**4g** (82)
7	homopiperazine (**3h**)[c]	0.5	**4h** (86)
8	2-methylpiperazine (**3i**)	3.5	**4i** (79)
9	decahydroquinoline (**3j**)	4	**4j** (92)

[a] Isolated yield. 4-Chloro-5-methoxypyridazin-3-one was also isolated in good yields. [b] *N*-Nitrsodicyclohexylamine (**4k**) was also isolated in 39% yield. [c] Reaction of **3h** with **2b** (2 equiv) in refluxing acetonitrile gave 1,4-dinitrohomopiperazine (**4l**) in 82% yield.

derivatives **2b** and **2d** showed excellent *N*-nitro transfer potentiality to secondary amine. For easy preparation of 4-chloro-5-methoxypyridazin-3-one, we selected compound **2b** as a new nitrating reagent. The solvent effect of this reaction was also examined, and the results are shown in Table 2 (entries 2 and 7−12). Dichloromethane, ethyl acetate, acetonitrile, and diethyl ether were good solvents for our system. *N*-Nitration of some secondary amines **3b**−**j** with **2b** as a nitrating agent at room temperature in dichloromethane gave the corresponding *N*-nitro derivatives **4b**−**c** and **4e**−**j** in good yield except for **3d** (Table 3). *N*-Nitration of dicyclohexylamine (**3d**) with **2b** in dichloromethane afforded **4d** as the minor product in 29% yield and *N*-nitrosodicyclohexylamine (**4k**) as the major product in 39% yield (Table 3, entry 3). The structure of **4k** was established by X-ray analysis

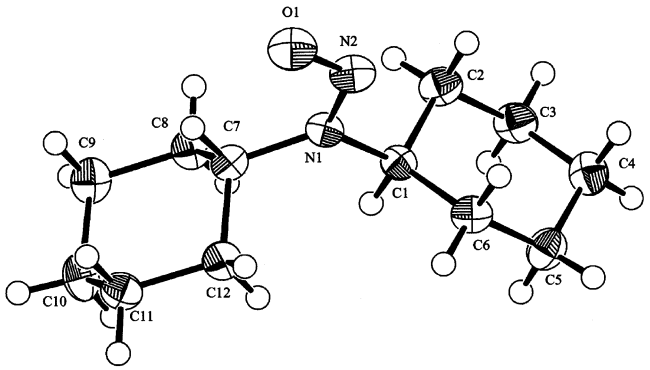
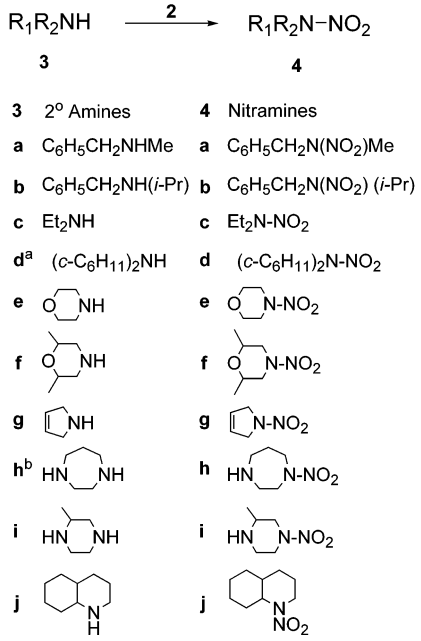


FIGURE 1. ORTEP of *N*-nitrosodicyclohexylamine (**4k**).

SCHEME 2



(Figure 1). According to TLC monitoring, compound **4d** changed slowly to the corresponding *N*-nitroso derivative **4k** under the reaction condition.

N-Nitration of homopiperazine (**3h**) with 2 equiv of **2b** at room temperature also yielded 1,4-dinitrohomopiperazine (**4l**) in 82% yield. On the other hand, *N*-nitration of primary amine, amide, and aromatic secondary amines was not achieved by using compound **2b**.

In conclusion, our method for *N*-nitration of aliphatic secondary amines using **2b** is novel, practical, and convenient. 2-Nitro-4-chloro-5-methoxypyridazin-3-one (**2b**) can act as a stable, mild, and efficient reagent as a source for the delivery of nitronium ion (NO_2^+) under mild, neutral, and homogeneous conditions.

Experimental Section

***N*-Nitration of 4-Chloro-5-methoxypyridazin-3-one.** A mixture of $Cu(NO_3)_2 \cdot 3H_2O$ (5 g, 21.5 mmol) and acetic anhydride (50 mL) was stirred for 1.2 h. After adding 4-chloro-5-methoxypyridazin-3-one (3 g, 18.7 mmol), the resulting mixture was stirred for an additional 2 h at room temperature. MeOH (150 mL) was added to the mixture, and the mixture was then stirred for an additional 0.5 h. After the solvent was evaporated, water (100 mL) was added. The solution was neutralized with an

aqueous saturated solution of sodium bicarbonate to pH 6. The precipitate was filtered, washed with water (500 mL), and dried in air to give 4-chloro-5-methoxy-2-nitropyridazin-3-one (**2b**) in 90% (3.4 g) yield.

General Procedure for *N*-Nitration of Secondary Amines by Using 2b. A secondary amine (3.4 mmol) was dissolved in methylene chloride (30 mL). After **2b** (0.7 g, 3.7 mmol) was added, the mixture was stirred and monitored by TLC until **2b** disappeared. The solvent was coevaporated with silica gel (2 g) under reduced pressure. The resulting silica gel was applied to the top of an open-bed silica gel column (2.5 × 7 cm). The column was eluted with ethyl acetate/*n*-hexane (1:3, v/v). Fractions containing *N*-nitramine were combined and the solvent was evaporated under reduced pressure to give the analytically pure corresponding *N*-nitramine. Reusable 4-chloro-5-methoxy-pyridazin-3-one was also isolated in quantitative yield.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data, IR spectral data, CHN analyses, and melting point for compounds **2** and **4**; X-ray analytical data for *N*-nitrosodicyclohexylamine (**4k**). This material is available free of charge via the Internet at http://pubs.acs.org.

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