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Efficient *N*-arylation of pyridazin-3(2*H*)-ones

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Abstract—A variety of substituted pyridazin-3(2*H*)-ones are directly *N*-arylated in good yield using lead tetraacetate/zinc chloride in benzene or in substituted benzenes including chloro- and bromobenzene.

There is considerable economic and biological interest in pyridazinones, many of which are known to possess useful activities in a variety of applications.[1–11] For instance, pyridazin-3(2*H*)-ones with heteroatoms at position 5, especially those with aryl substituents at N-2, show potent herbicidal activity, for example, Chloridazon,[1,5,6,9] BAS 44521,[1,9] Norflurazon[1,7,9] and Pyridate.[9] Typically, 2-phenylpyridazin-3(2*H*)-ones are synthesized using phenylhydrazine or the corresponding phenylhydrazones,[12–18] and phenyldiazonium salts.[9,19,20] During the reaction of hydrazines with maleic anhydrides, however, *N*-aminomaleimides are formed as a by-product.[20] Also, 2-phenyl-4,5-disubstituted-pyridazin-3(2*H*)-ones are often transformed into pyrazoles under the vigorous conditions required for their preparation.[21] The low yields of 2-phenylpyridazin-3(2*H*)-ones may be due to the above-mentioned side reactions during the condensation of phenylhydrazines with mucochloric acids. The direct *N*-arylation of heterocycles[22] represents an attractive alternative synthetic strategy that would obviate the aforementioned problems, although to the best of our knowledge, this approach has not been applied to substituted pyridazin-3(2*H*)-ones.

Most direct N-arylations of NH-containing heteroarenes are achieved by one of four methods: (i) catalytic copper iodide/haloarene/ligand/base;[22,23] (ii) cupric acetate/arylboronic acids,[24] arylsiloxanes[25] or aryllead triacetate[26]/base; (iii) catalytic cupric trifluoroacetate/triphenylbismuth bistrifluoroacetate[27] or catalytic cupric acetate/triphenylbismuth bistrifluoroacetate;[28] or (iv) Pd catalysts/ligand/base.[29]

While all of these methods are useful in their own right, each suffers from one or more limitations including a lack of generality, poor yields with halogenated substrates, or incompatibility with base-sensitive compounds. Additionally, the preparation of aryllead triacetates via metal exchange with arylmercury or tin is especially inconvenient.[30] Herein, we report the efficient *N*-arylation of substituted-pyridazin-3(2*H*)-ones with benzene or benzene derivatives in the presence of lead tetraacetate/zinc chloride (Scheme 1).

Firstly, we evaluated the direct *N*-phenylation of 4,5-dichloropyridazin-3(2*H*)-one (**1a**) using varying amounts of lead tetraacetate in refluxing benzene (Table 1). Treatment of **1a** with 0.5 equiv of lead tetraacetate gave 4,5-dichloro-2-phenylpyridazin-3(2*H*)-one (**2a**) in 32% yield, whereas 1.0–4.0 equiv of lead tetraacetate boosted the yield of **2a** moderately (50–57%).

To further increase the yield, the influence of different acids and bases on the *N*-phenylation of **1a** using lead tetraacetate (1.2 equiv) in refluxing benzene was studied (Table 2). Most bases (entries 1–4) interfered or completely suppressed with the reaction. NaH (entry 5)

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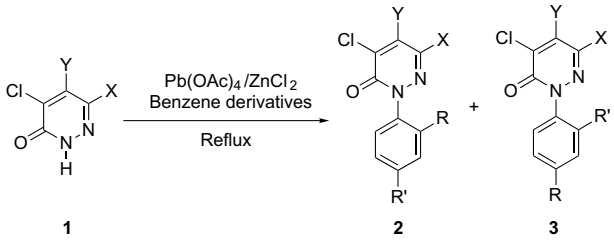

1 2 3

1-3	X	Y	2,3	X	Y	R	R'	2,3	X	Y	R	R'
a	H	Cl	a	H	Cl	H	H	h	H	Cl	Me	Me
b	H	OMe	b	H	OMe	H	H	i	H	Cl	NO_2	H
c	H	N_3	c	H	N_3	H	H	j	H	Cl	Cl	H
d	H	OPh	d	H	OPh	H	H	k	H	Cl	Br	H
e	NO_2	Cl	e	NO_2	Cl	H	H	l	H	Cl	OMe	H
f	Cl	Cl	f	Cl	Cl	H	H	m	H	Cl	N(Me)CHO	H
			g	H	Cl	Me	H					

Scheme 1.

Table 1. *N*-Phenylation of 4,5-dichloropyridazin-3(2*H*)-one (**1a**) using varying amounts of lead tetraacetate without $ZnCl_2$

Entry	$Pb(OAc)_4$ (equiv)	Time (h)	**2a** (Yield, %)[a]
1	0.5	50	32
2	1.0	32	50
3	2.0	33	55
4	4.0	35	57

[a] Isolated yield.

seemed to have little effect. In contrast, stoichiometric amounts of $ZnCl_2$ were quite helpful (entries 6–9), with the maximum benefit occurring with 1 equiv. Interestingly, other Lewis acids were detrimental (entries 10–13).

The applicability of lead tetraacetate/zinc chloride in refluxing benzene for the *N*-phenylation of more highly substituted pyridazin-3(2*H*)-ones was also investigated (Table 3).

Table 2. *N*-Phenylation of 4,5-dichloropyridazin-3(2*H*)-one (**1a**) using lead tetraacetate (1.2 equiv) in the presence of a base or an acid

Entry	Base or acid	Equivalent	Time (h)	**2a** (Yield, %)[a]
1[b]	K_2CO_3	1.0	24	25
2[b]	Cs_2CO_3	1.0	24	14
3	Et_3N	1.0	48	No reaction
4	DMAP[c]	1.0	26	No reaction
5[b]	NaH	1.0	23	55
6	$ZnCl_2$	0.2	48	54
7	$ZnCl_2$	0.5	30	70
8	$ZnCl_2$	1.0	20	75
9	$ZnCl_2$	2.0	20	61
10	$AlCl_3$	1.0	20	—[d]
11	$FeCl_3$	1.0	20	—[d]
12	$TiCl_4$	1.0	30	No reaction
13	$BF_3{\cdot}OEt_2$	1.0	30	No reaction

[a] Isolated yields.
[b] Starting material was recovered.
[c] 4-(*N*,*N*-Dimethylamino)pyridine.
[d] Unknown products were also detected.

Table 3. *N*-Phenylation of 4-chloropyridazin-3(2*H*)-ones using lead tetraacetate (1.2 equiv)/$ZnCl_2$ (1 equiv)

Entry	Pyridazin-3(2*H*)-ones	Time (h)	**2** (Yield, %)[a]
1	**1b**	25	**2b** (68)
2	**1c**	25	**2c** (55)
3[b]	**1d**	21	**2d** (37)
4	**1e**	15	**2e** (71)
5[b]	**1f**	19	**2f** (59)

[a] Isolated yields.
[b] An unknown product was also detected.

4-Chloro-5-methoxypyridazin-3(2*H*)-one (**1b**) gave **2b** in 68% yield, 5-azido-4-chloropyridazin-3(2*H*)-one (**1c**) furnished **2c** in 55% yield, and the 4,5,6-trisubstituted-pyridazin-3(2*H*)-ones **1d**, **1e** and **1f** led to **2d** (37%), **2e** (71%) and **2f** (59%), respectively.

Encouraged by the preceding results, the combination of lead tetraacetate/zinc chloride was exploited for the *N*-arylation of pyridazinones **1** using various substituted benzenes to afford 2-phenylpyridazin-3(2*H*)-ones **2** and **3** (Table 4). As anticipated, toluene gave a regioisomeric mixture of **2g** (32%) and **3g** (22%) whereas *m*-xylene evolved just **2h** (65%).

Even nitrobenzene, which is unreactive towards electrophilic substitution, yielded **2i** (27%) and **3i** (34%). Chlorobenzene furnished **2j** (30%) and **3j** (46%) and bromobenzene analogously gave rise to **2k** (24%) and **3k** (28%). Methoxybenzene gave **2l** (38%) and **3l** (29%). Notably, *N*-methyl-*N*-phenylformamide furnished **3m** (57%) exclusively.

In view of the results, the $C(sp_2)$–N coupling under our system occurs between a C–H bond of benzene and the N–H bond of pyridazin-3(2*H*)-one.

In summary, we have developed an efficient, convenient and direct procedure for the *N*-arylation of pyridazin-3(2*H*)-ones using a wide variety of substituted benzenes. The catalyst system is compatible with a range of functional groups including phenyl bromides and chlorides. Further studies involving the application for other nitrogen heterocycles containing NH and the detailed mechanism are underway in our laboratory.

General procedures and data for *N*-Arylation, **2**: A mixture of lead tetraacetate (2.0 mmol) in aryl derivatives was slowly added pyridazine-3(2*H*)-one (1.82 mmol)

Table 4. *N*-Arylation of 4,5-dichloropyridazin-3(2*H*)-one (**1a**) using lead tetraacetate (1.2 equiv)/$ZnCl_2$ (1 equiv) in refluxing substituted benzene

Entry	Substituted benzene	Time (h)	Products	Yield (%)[a]
1	Toluene	20	**2g** (32)	**3g** (22)
2	*m*-Xylene	25	**2h** (65)	—
3	Nitrobenzene	11	**2i** (27)	**3i** (34)
4	Chlorobenzene	40	**2j** (30)	**3j** (46)
5	Bromobenzene	39	**2k** (24)	**3k** (28)
6	Methoxybenzene	20	**2l** (38)	**3l** (29)
7	*N*-Methyl-*N*-phenylformamide	10	—	**3m** (57)

[a] Isolated yields.

and zinc chloride (1.82 mmol). The mixture was stirred for 10 min and than refluxed for 20–48 h until pyridazine-3(2*H*)-one disappeared. After filtering the reaction mixture, the solvent was evaporated under reduced pressure, and the resulting residue was applied to the top of an open-bed silica gel column (3 × 10 cm), and the column was eluted with CH_2Cl_2/*n*-hexane = 2:1 (v/v). The fractions containing product were combined and evaporated under reduced pressure to afford the corresponding *N*-aryl pyridazin-3(2*H*)-one **2** in good yields.

4,5-Dichloro-2-phenylpyridazin-3(2*H*)-one (**2a**): White solid; mp 161–162 °C; R_f (CH_2Cl_2) = 0.67; IR (KBr) 3272, 3050, 2922, 1652, 1544, 1408, 1296, 1084, 1072, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91 (s, 1H), 7.59–7.56 (m, Aro–2H), 7.50–7.47 (m, Aro–2H), 7.44–7.42 (m, Aro–1H); ^{13}C NMR ($CDCl_3$) δ 125.18, 128.89, 128.95, 135.36, 136.11, 136.37, 140.90, 176.63. Anal. Calcd for $C_{10}H_6Cl_2N_2O$: C, 49.82; H, 2.51; N, 11.62. Found: C, 49.75; H, 2.39; N, 11.59.

4-Chloro-5-methoxy-2-phenylpyridazin-3(2*H*)-one (**2b**): White solid; mp 153–154 °C; R_f (CH_2Cl_2) = 0.28; IR (KBr) 3070, 2970, 2880, 1645, 1610, 1480, 1460, 1400, 1300, 1240, 1150, 1100, 950, 830, 760, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.58–7.54 (m, Aro–2H), 7.50–7.39 (m, Aro–3H), 4.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 57.82, 117.29, 125.36, 127.13, 128.51, 128.80, 141.29, 154.70, 158.30. Anal. Calcd for $C_{11}H_9ClN_2O_2$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.78; H, 3.92; N, 11.99.

5-Azido-4-chloro-2-phenylpyridazin-3(2*H*)-one (**2c**): White solid; mp. 99–100 °C; R_f (CH_2Cl_2) = 0.38; IR (KBr) 3070, 2980, 2950, 2890, 2150, 1660, 1600, 1500, 1380, 1330, 1310, 1150, 840, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (s, 1H), 7.58–7.55 (m, Aro–2H), 7.51–7.41 (m, Aro–3H); ^{13}C NMR ($CDCl_3$) δ 123.35, 125.17, 128.70, 128.86, 130.27, 139.11, 140.96, 156.81. Anal. Calcd for $C_{10}H_6ClN_5O$: C, 48.50; H, 2.44; N, 28.28. Found: C, 48.54; H, 2.45; N, 28.32.

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Supplementary data

Supplementary data associated with this article can found, in the online version, at doi:10.1016/j.tetlet.2004.10.003.

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