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Synthesis of Functionalized Pyridazin-3(2*H*)-ones via Bromine−Magnesium Exchange on Bromopyridazin-3(2*H*)-ones

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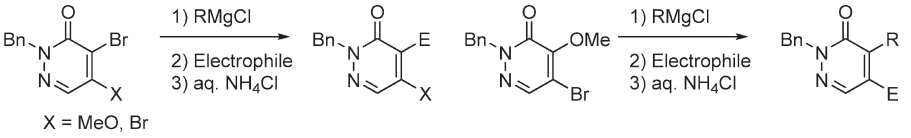

The potential of halogen−magnesium exchange reactions, followed by quenching with electrophiles, for the functionalization of the pyridazin-3(2*H*)-one core was investigated. 2-Benzyl-4-bromo-5-methoxy- (**1**), 2-benzyl-5-bromo-4-methoxy- (**4**), and 2-benzyl-4,5-dibromopyridazin-3(2*H*)-one (**10**) were selected as readily available model substrates. While **1** and **10** gave exclusively C-4 metalation, a tandem reaction involving nucleophilic substitution via addition elimination and bromine−magnesium exchange was observed with **4**.

Introduction

Polyfunctionalized pyridazines are of considerable importance due to their application as drugs (e.g., Minaprine), pesticides (e.g., Pyridaben), and advanced materials (e.g., polymers and oligomers with interesting optical and electrochemical properties).[1] The number of synthetic methods hitherto available to functionalize the 1,2-diazine skeleton is rather limited due to the high π-deficient character of the heterocycle.[1] Pyridazine derivatives are therefore only sufficiently reactive for electrophilic substitution when one or more electron donating substituents are present. Consequently, they are very susceptible for nucleophilic attack. Minisci reactions involving nucleophilic radicals are well explored and smooth alkylation, acylation, benzoylation, and alkoxycarbonylation has been reported.[1c,d,2] Monofunctionalization and regioselectivity problems sometimes hamper the efficiency of this process. Functionalization of halopyridazine derivatives with nucleophiles (O, N, S) via S_NAE (= nucleophilic substitution via addition elimination) reactions is certainly the most documented reaction involving nucleophilic reagents.[1] Because of the electron deficient nature, halopyridazines (even chlorinated derivatives) can also smoothly undergo carbon−carbon bond forming reaction via Pd-catalyzed reactions.[1c,d,3,4] This had a major impact as alkyl, alkenyl, alkynyl, aryl, alkoxycarbonyl, and aminocarbonyl moieties can be installed in an efficient way. An even more attractive approach for functionalization is the synthesis of metalated 1,2-diazines, which upon

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(3) For reviews dealing with Pd-catalyzed reactions on halopyridazines and halopyridazin-3(2*H*)-ones see: (a) Maes, B. U. W.; Tapolcsányi, P.; Meyers, C.; Mátyus, P. *Curr. Org. Chem.* **2006**, *10*, 377. (b) Maes, B. U. W. In *Palladium in Heterocyclic Chemistry*; Tetrahedron Organic Chemistry Series; Li, J. J., Gribble, G. W., Eds.; Elsevier: New York, 2006, Vol. 26, p 541.

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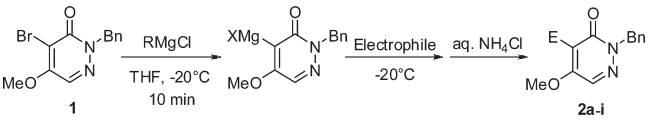
quenching with electrophiles (with or without the aid of a transition metal catalyst or prior transmetalation with a metal salt) allow the direct introduction of an even wider variety of functional groups. Investigation of the metalation (Li) and metal (Li, Mg)−halogen (I, Br) exchange on (halo)-pyridazines has been reported.[5−7] Surprisingly, for the important pyridazin-3(2*H*)-one subclass, only Li−halogen exchange (I, Br) has been hitherto investigated.[4j] 4-Iodo-5-methoxy-2-methyl-, 2-substituted (Me, Et, *t*-Bu, Ph) 4-bromo-5-methoxy-, and 5-chloro-4-iodo-2-methylpyridazin-3(2*H*)-one were used as substrates with *n*-BuLi as exchange reagent at −70 °C in THF. Benzaldehydes, Me_3SnCl, MeI, D_2O, and CO_2 proved to be suitable electrophiles, but DMF for instance not. The more covalent character of a carbon−magnesium bond allowing a wider functional group compatibility, the possibility to work at higher temperatures and the absence of literature data on halogen-magnesium exchange reactions involving halopyridazin-3(2*H*)-ones inspired us to perform such a study. 2-Benzyl-4-bromo-5-methoxy- (**1**), 2-benzyl-5-bromo-4-methoxy- (**4**), and 2-benzyl-4,5-dibromopyridazin-3(2*H*)-one (**10**) were selected as test substrates. The choice for an *N*-benzyl protective group is based on its potential removal after functionalization.[8]

Results and Discussion

We started our study by comparing three commercially available RMgCl (2M in THF) reagents (*n*-BuMgCl, *i*-PrMgCl, and PhMgCl) in the bromine−magnesium exchange reaction on 2-benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (**1**). The efficiency of these reagents was evaluated by quenching the reaction mixture with D_2O as electrophile and comparing the isolated yields of 2-benzyl-4-deutero-5-methoxypyridazin-3(2*H*)-one (**2a**). When *n*-BuMgCl and *i*-PrMgCl were used, no substrate remained when performing bromine−magnesium exchange for 10 min at −20 °C followed by hydrolysis with D_2O. The yield of **2a** was 95% for the reaction with *n*-BuMgCl and 83% with *i*-PrMgCl (Table 1, entries 1 and 2), pointing at the former as the most efficient reagent. PhMgCl was also tested but, as expected, found to be much slower in the halogen−metal exchange process. Two equiv of PhMgCl as well as an increase of the reaction time to 90 min were required to achieve complete conversion of **1**. In addition, the isolated yield of **2a** (71%) was substantially lower than that obtained with the alkylmagnesium chlorides (Table 1, entry 3). Attempts to use *t*-BuMgCl as reagent and D_2O as quenching agent completely failed. Even when 2 equiv of *t*-BuMgCl were used, some starting material (**1**) always remained. Moreover, the main reaction product was 2-benzyl-5-methoxypyridazin-3(2*H*)-one (**2b**), presumably formed via dehydrohalogenation of the in situ created *t*-butyl halide by (2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)magnesium halide.

TABLE 1. Functionalization of Pyridazin-3(2*H*)-ones via Bromine−Magnesium Exchange on 2-Benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (1)[a]



1 **2a-i**

entry	RMgCl	electrophile	E	**2**	yield (%)
1	*n*-BuMgCl	D_2O	D	**2a**	95
2	*i*-PrMgCl	D_2O	D	**2a**	83
3	PhMgCl	D_2O	D	**2a**	71[b]
4	*n*-BuMgCl	PhCHO	PhCH(OH)	**2c**	43
5	*n*-BuMgCl	Ph_2CO	$Ph_2C(OH)$	**2d**	62
6	*i*-PrMgCl	Ph_2CO	$Ph_2C(OH)$	**2d**	48
7	PhMgCl	Ph_2CO	$Ph_2C(OH)$	**2d**	66[b]
8	*n*-BuMgCl	PhCOCOOMe	PhC(OH)COOMe	**2e**	43
9	*n*-BuMgCl	DMF	HCO	**2f**	66
10	*n*-BuMgCl	$HCON(CH_2)_5$	HCO	**2f**	52
11	*n*-BuMgCl	TsCN	CN	**2g**	46
12	*n*-BuMgCl	MeSSMe	SMe	**2h**	57[c]
13	*n*-BuMgCl	I_2	I	**2i**	79

[a] **1** (1 mmol), 0.5 mL 2M RMgCl (1 equiv), THF (4 mL), −20 °C, 10 min; electrophile (1 equiv); aq NH_4Cl. [b] 1 mL 2M PhMgCl (2 equiv) and a bromine−magnesium exchange reaction time of 90 min were used. [c] 2-Benzyl-4,5-bis(methylthio)pyrdiazin-3(2*H*)-one (**2o**) (18%) was also isolated.

Next, we investigated the optimal time for bromine−magnesium exchange by taking samples after 1, 5, 10, 30, and 60 min reaction time and quenching these with D_2O. Qualitative MS-analysis of these samples (relative intensity of signals from **2a** and **2b**) revealed that the amount of incorporated deuterium versus hydrogen gradually reduced as a function of time. This is probably due to a reaction of (2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)magnesium halide with the alkyl halide formed in the halogen−metal exchange reaction. With *n*-BuMgCl at −20 °C a 1:1 ratio **2a**/**2b** was observed after 60 min. No deuterium incorporation could be detected after 2 h. For reaction with *i*-PrMgCl, the point of no deuterium incorporation was already obtained after 1 h. The presence of β-hydrogens in the alkyl halide formed, which allows elimination, seems to be crucial for the stability of (2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)magnesium halide. This was confirmed by reacting **1** with PhMgCl at −20 °C, as after stirring overnight no hydrogen incorporation was detected. Our quenching experiments with D_2O revealed that the exchange reaction with *n*-BuMgCl and *i*-PrMgCl is fast. The subsequent reaction with electrophiles will therefore require its rapid addition. An exchange time of around 10 min proved to be optimal.

With optimal bromine−magnesium exchange reaction conditions in hand (1 equiv *n*-BuMgCl, THF, −20 °C, 10 min),

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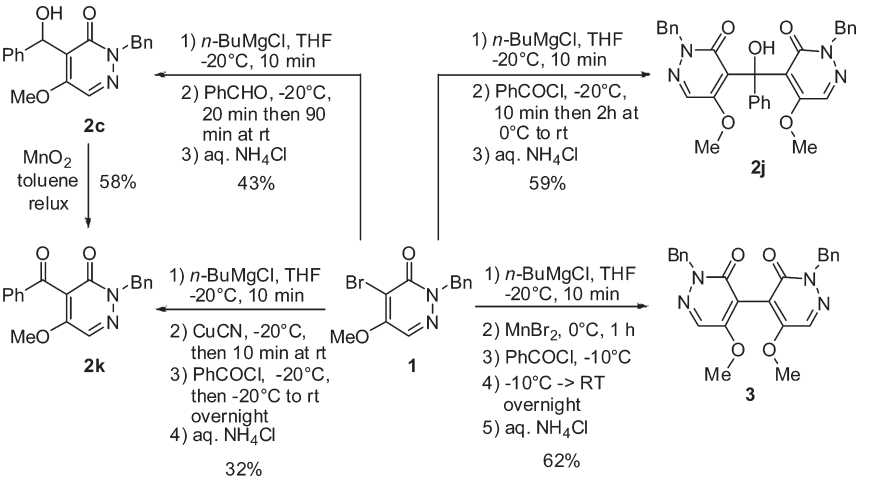
(7) The scope of the process is unfortunately usually limited to electron rich pyridazines avoiding competitive addition reactions. For the addition reaction of *s*-BuLi on pyridazines and pyridazin-3(2*H*)-ones see Dal Piaz, V.; Capperucci, A. *Synlett* **1998**, 762.

(8) Riedl, Z.; Maes, B. U. W.; Monsieurs, K.; Lemière, G. L. F.; Mátyus, P.; Hajós, G. *Tetrahedron* **2002**, *58*, 5645.

SCHEME 1. Attempted Syntheses of 4-Benzoyl-2-benzyl-5-methoxypyridazin-3(2*H*)-one (2k) via Bromine−Magnesium Exchange on 2-Benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (1)



we tested a variety of electrophiles. Benzaldehyde, benzophenone, methyl oxo(phenyl)acetate, DMF, *N*-formylpiperidine, TsCN, Me_2S_2, and I_2 gave the corresponding 4-[hydroxy(phenyl)methyl] (**2c**), 4-[hydroxy(diphenyl)methyl] (**2d**), 4-(2-methoxy-1-hydroxy-2-oxo-1-phenylethyl) (**2e**), 4-formyl (**2f**), 4-cyano (**2g**), 4-methylthio- (**2h**), and 4-iodo- (**2i**) substituted pyridazin-3(2*H*)-ones in good to excellent yields (Table 1, entries 4, 5, 8−13). For benzophenone as electrophile, the three RMgCl exchange reagents were again compared, confirming that *n*-BuMgCl gives a better result than *i*-PrMgCl as observed for D_2O (Table 1, entries 5 and 6). In this case, an equal yield could be obtained with PhMgCl (Table 1, entry 7). The reaction with benzoyl chloride provided 4,4′-[hydroxy(phenyl)methylene]bis(2-benzyl-5-methoxypyridazin-3(2*H*)-one) (**2j**), even with a 10-fold excess of benzoyl chloride (Scheme 1). 4-Benzoyl-2-benzyl-5-methoxypyridazin-3(2*H*)-one (**2k**) could be obtained via prior transmetalation of (2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)magnesium halide to the corresponding organocopper reagent via reaction with CuCN, followed by reaction with benzoyl chloride (Scheme 1).[9] Alternatively, the 4-benzoyl derivative **2k** was obtained by oxidation of alcohol **2c** with MnO_2.[4j] Interestingly, homo coupled product 2,2′-dibenzyl-5,5′-dimethoxy-4,4′-bipyridazine-3,3′(2*H*,2′*H*)-dione (**3**) was the main reaction product when a transmetalation with $MnBr_2$ instead of Cu(I)CN was attempted (Scheme 1).[10] These homocoupled pyridazinones represent to the best of our knowledge a new class of compounds.

The reaction of (2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)magnesium halide with DMF or *N*-formylpiperidine as electrophiles proved to be very interesting, as a different reaction product was obtained depending on the workup procedure applied (Scheme 2). When the reaction is worked up by pouring it quickly into a big amount of a saturated aq NH_4Cl solution, the main reaction product is the expected 2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (**2f**). If the reaction mixture is, however, treated with dry MeOH, prior to adding aq NH_4Cl solution, 2-benzyl-5-(dimethylamino)-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (**2l**) and 2-benzyl-3-oxo-5-piperidin-1-yl-2,3-dihydropyridazine-4-carbaldehyde (**2m**) are obtained as the reaction products resulting from respectively the use of DMF and *N*-formylpiperidine as electrophile.[11] This can be rationalized by considering how the intermediate deprotonated hemiaminal **A** is decomposed upon adding a proton source (Scheme 3). When saturated aq NH_4Cl is used, **A** gets immediately *O*- and *N*-protonated in the low pH medium forming **B**, followed by extrusion of dimethylamine or piperidine, which will be immediately protonated, hereby losing its nucleophilic properties. Upon using MeOH as proton source, the deprotonated heminal **A** can only be *O*-protonated due to the much higher pH of the mixture. Collapse of the hemiaminal **C** therefore in this case will deliver dimethylamine or piperidine, which subsequently reacts in C-5 of the formed pyridazin-3(2*H*)-one **2f**. This mechanism is supported by an independent reaction of **2f** with dimethylamine in MeOH at room temperature, giving a smooth conversion to **2l** (99% yield). Interestingly, when MeSNa was added after the addition of DMF electrophile workup of the reaction mixture with aq NH_4Cl revealed the presence of 2-benzyl-5-(methylthio)-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (**2n**), indicating that even C-5 of **A** is susceptible for intermolecular nucleophilic attack (Scheme 2). The susceptibility of the C-5 methoxy group in pyridazin-3(2*H*)-ones for nucleophilic substitution is independently shown by the reaction of (2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)magnesium halide with dimethyldisulfide, as besides 57% of expected 2-benzyl-5-methoxy-4-(methylthio)pyridazin-3(2*H*)-one (**2h**), also 18% of 2-benzyl-4,5-bis(methylthio)pyridazin-3(2*H*)-one (**2o**) was isolated (Table 1, entry 12). The latter can be rationalized by nucleophilic attack of in situ formed methylthiolate on the reaction product **2h**.[12]

Subsequently, we investigated 2-benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one (**4**), an isomer of **1**, as substrate.

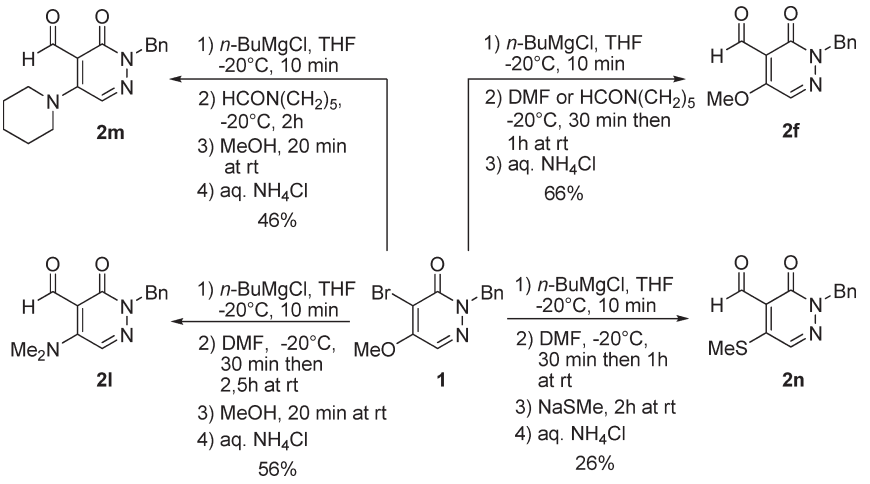
(9) Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Org. Chem.* **2001**, *66*, 2302.

(10) Cahiez, G.; Rivas-Enterrios, J.; Clery, P. *Tetrahedron Lett.* **1988**, *29*, 3659.

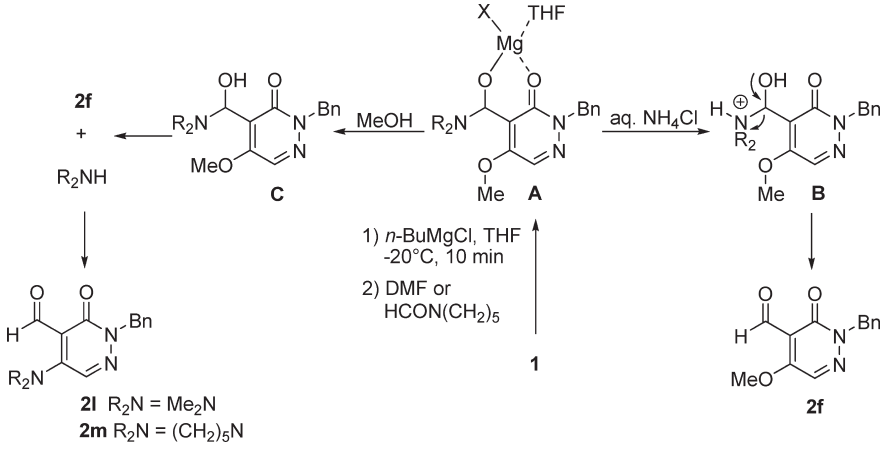
(11) A similar reaction involving the additional substitution of a C-4 halogen by a dimethylamino group was observed when using 3,6-dimethoxy-4,5-diodo- and 3,6-dimethoxy-4,5-dibromopyridazine as substrates, *i*-PrMgCl as halogen−magnesium exchange reagent and DMF as the electrophile: see ref 5f.

(12) For ipso substitutions in (η^6-arene)tricarbonylchromium, see: Rose-Munch, F.; Rose, E. *Eur. J. Inorg. Chem.* **2002**, *6*, 1269.

SCHEME 2. Dependence of the Reaction Product Formation on the Workup Procedure after Quenching of (2-Benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)magnesium halide with DMF or *N*-Formylpiperidine

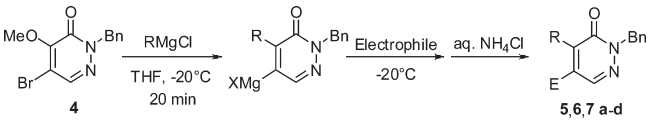


SCHEME 3. Plausible Mechanism Explaining the Different Reaction Products Obtained when a Workup with MeOH or aq NH_4Cl was Performed



When applying the optimal reaction conditions identified for bromine−magnesium exchange on **1** (1 equiv *n*-BuMgCl, THF, −20 °C, 10 min) on **4**, a remarkable observation was made. Quenching with D_2O as electrophile revealed the formation of 2-benzyl-4-butyl-5-deuteropyridazin-3(2*H*)-one (**5a**). Apparently, an S_NAE reaction in C-4 as well as a bromine−magnesium exchange in C-5 occurred in a single reaction step. As this process requires at least 2 equiv of *n*-BuMgCl to achieve complete conversion, we subsequently performed the reaction with 3 equiv of exchange reagent and applied an extended reaction time of 20 min before the addition of the electrophile. This resulted in a complete conversion of **4** and an isolated yield of 22% of **5a** (Table 2, entry 1). A similar reaction protocol with *i*-PrMgCl gave 61% of 2-benzyl-5-deutero-4-isopropylpyridazin-3(2*H*)-one (**6a**) (Table 2, entry 2). With PhMgCl, which is less nucleophilic and slower in bromine−magnesium exchange reactions, 4 equiv of organomagnesium reagent and a reaction time of 90 min were used before the electrophile was added. This gave 2-benzyl-5-deutero-4-phenylpyridazin-3(2*H*)-one (**7a**) in 18% yield (Table 2, entry 3). Next, the generality of the tandem protocol was tested with a variety of electrophiles using *n*-BuMgCl and *i*-PrMgCl as well as PhMgCl as Grignard reagents. Benzaldehyde, methyl oxo(phenyl)acetate, and Me_2S_2 gave the corresponding 5-[hydroxy(phenyl)methyl] (**5b**, **6b**, **7b**), 5-(2-methoxy-1-hydroxy-2-oxo-1-phenylethyl) (**5c**, **6c**, **7c**), and 5-(methylthio)-(**5d**, **6d**, **7d**) substituted 4-alkyl or 4-phenyl-2-benzylpyridazin-3(2*H*)-ones in good to excellent yields by taking into account that two reactions occurred in one synthetic step (Table 2, entries 4−12). We believe that the carbonyl of the lactam function of the substrate coordinates the RMgX compound. Hereby the nucleophilicity of the Grignard reagent is increased (ionic character) as well as the electrophilicity of C-4 (inductive effect), both favoring nucleophilic addition reaction at C-4 of the pyridazin-3(2*H*)-one. Moreover, the coordination creates a proximity effect of the R group toward C-4. Interestingly, the bromine−magnesium exchange reaction at C-5 could be completely suppressed when a lower reaction temperature was selected pointing at S_NAE as the fastest step of the tandem protocol. This is exemplified by a reaction of *n*-BuMgCl with **4** at −78 °C. Even with a 3-fold excess of *n*-BuMgCl, only 2-benzyl-5-bromo-4-butylpyridazin-3(2*H*)-one (**8**) was obtained in an excellent yield (83%). With less nucleophilic PhMgCl, bromine−magnesium exchange and S_NAE become more

TABLE 2. Tandem Functionalization of Pyridazin-3(2*H*)-ones via S_NAE and Bromine−Magnesium Exchange on 2-Benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one (4)[a]



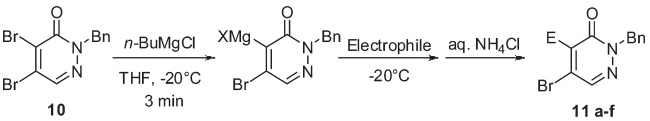
entry	RMgCl	electrophile	E	5, 6, 7	yield (%)
1	*n*-BuMgCl	D_2O	D	**5a**	22
2	*i*-PrMgCl	D_2O	D	**6a**	61
3	PhMgCl	D_2O	D	**7a**	18[b]
4	*n*-BuMgCl	PhCHO	PhCH(OH)	**5b**	43
5	*i*-PrMgCl	PhCHO	PhCH(OH)	**6b**	76
6	PhMgCl	PhCHO	PhCH(OH)	**7b**	73[b]
7	*n*-BuMgCl	PhCOCOOMe	PhC(OH)COOMe	**5c**	56
8	*i*-PrMgCl	PhCOCOOMe	PhC(OH)COOMe	**6c**	72
9	PhMgCl	PhCOCOOMe	PhC(OH)COOMe	**7c**	31[b]
10	*n*-BuMgCl	MeSSMe	SMe	**5d**	54
11	*i*-PrMgCl	MeSSMe	SMe	**6d**	70
12	PhMgCl	MeSSMe	SMe	**7d**	78[b]

[a] **4** (1 mmol), 1.5 mL 2M RMgCl (3 equiv), THF (4 mL), −20 °C, 20 min; electrophile (2,5−11 equiv); aq NH_4Cl. [b] 2 mL 2M PhMgCl (4 equiv) and a bromine−magnesium exchange reaction time of 90 min were used.

similar in reaction rate at the same temperature, the latter being still favored. This is supported by the reaction of **4** with PhMgCl at −78 °C using benzaldehyde as the quenching electrophile because besides 67% of 2-benzyl-5-[hydroxy(phenyl)methyl]-4-phenylpyridazin-3(2*H*)-one (**7b**) also 23% of 2-benzyl-5-[hydroxy(phenyl)methyl]-4-methoxypyridazin-3(2*H*)-one (**9**) was obtained after workup.

Finally, we wondered whether C-4 regioselective bromine−magnesium exchange in 2-benzyl-4,5-dibromopyridazin-3(2*H*)-one (**10**) would be a feasible process. On the basis of the presumed anchoring of the RMgX reagent via coordination with the lactam function of the substrate, a C-4 preference was theoretically expected.[13] As for substrate **1**, the optimal time for bromine−magnesium exchange was determined by taking samples which were subsequently quenched with D_2O. Analysis of these samples with mass spectroscopy revealed that a reaction time of only 3 min is optimal for the removal of one bromine atom in **10** (Table 3, entry 1). Bromine−magnesium exchange of **10** with 1 equiv *n*-BuMgCl in THF followed by quenching with H_2O gave 55% of 2-benzyl-5-bromopyridazin-3(2*H*)-one (**11b**) (Table 3, entry 2). Exclusive formation of **11b** revealed that C-4 regioselective exchange can indeed be achieved on **10**. **11b** could easily be distinguished from its regioisomer 2-benzyl-4-bromopyridazin-3(2*H*)-one based on its specific ^4J coupling constant between H-4 and H-6.[1] An X-ray confirmed the structure. Interestingly, as in substrate **1**, S_NAE is no competitive reaction, as only traces of 4-butyl substituted pyridazin-3(2*H*)-ones could be observed in the crude reaction mixture. With optimal reaction conditions in hand (1 equiv *n*-BuMgCl, THF, −20 °C, 3 min), a variety of

TABLE 3. Functionalization of Pyridazin-3(2*H*)-ones via Regioselective Bromine−Magnesium Exchange on 2-Benzyl-4,5-dibromopyridazin-3(2*H*)-one (10)[a]



entry	electrophile	E	11	yield (%)
1	D_2O	D	**11a**	44
2	H_2O	H	**11b**	55
3	PhCHO	CH(OH)Ph	**11c**	49
4	DMF	CHO	**11d**	78
5	Ph_2CO	$Ph_2C(OH)$	**11e**	80
6	MeSSMe	SMe	**11f**	0[b]

[a] **1** (1 mmol), 0.5 mL 2M RMgCl (1 equiv), THF (4 mL), −20 °C, 3 min; electrophile (2 equiv); aq NH_4Cl. [b] Only 2-benzyl-4,5-dimethylthiopyridazin-3(2*H*)-one (**2o**) was isolated (58%).

electrophiles were subsequently tested. Benzaldehyde, DMF, and benzophenone gave the corresponding 4-[hydroxy(phenyl)methyl] (**11c**), 4-formyl (**11d**), and 4-[hydroxy(diphenyl)methyl] (**11e**) substituted pyridazin-3(2*H*)-ones in good to excellent yields (Table 3, entries 3−5). When using DMF as the electrophile treatment of the reaction mixture with dry MeOH, prior to adding aq NH_4Cl solution, gave 47% 2-benzyl-5-(dimethylamino)-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (**2l**) instead of 2-benzyl-5-bromo-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (**11d**). The same behavior was observed with substrate **1** when dry MeOH was used as the proton source (Scheme 2). The use of dimethyldisulfide as electrophile gave exclusively 2-benzyl-4,5-bis(methylthio)pyridazin-3(2*H*)-one (**2o**) and no 2-benzyl-5-bromo-4-(methylthio)pyridazin-3(2*H*)-one (**11f**) was formed (Table 3, entry 6). On the basis of the reaction of substrate **1** with *n*-BuMgCl, using the same electrophile as quencher, this result is not surprising as in that case a methoxy group could be smoothly substituted by the in situ formed methylthiolate nucleophile (Table 1, entry 12).

Conclusion

Our results show that bromine−magnesium exchange on bromopyridazin-3(2*H*)-ones is a new and interesting way to achieve efficient functionalization of the pyridazin-3(2*H*)-one core. Regioselective exchange as well as tandem functionalizations could be achieved as exemplified on substrate **10** and **4**, respectively. As a diverse set of groups can be easily introduced using this methodology, the identified protocols will allow to synthesize a wide variety of new substituted pyridazin-3(2*H*)-ones (involving functionalities hitherto largely unexplored) with potential applications in pharmaceutical chemistry, agrochemistry, and material science.[14]

Experimental Section

General Procedure 1 for the Functionalization of Pyridazin-3(2*H*)-ones via Bromine−Magnesium Exchange with RMgCl on 2-Benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one (1). Bromopyridazin-3(*H*)-one **1** (0.295 g, 1 mmol) was brought in a

(13) For regioselective bromine−magnesium exchange in dibromopyridines, see: Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349. For regioselective bromine−magnesium exchange in 4,5-dibromo-2,6-dimethoxypyrimidine see: Boudet, N.; Knochel, P. *Org. Lett.* **2006**, *8*, 3737.

(14) A Scifinder database search revealed that 70% of the molecules synthesized in this manuscript (with the specific substituents on C-4 and C-5 shown in the tables, schemes and figures, leaving the *N*-2 and *C*-6 substituents undefined) were hitherto unknown.

50 mL two-necked round-bottomed flask and put under argon atmosphere making use of a Schlenk apparatus. Subsequently, 4 mL of THF was added and the solution was cooled to −20 °C (ice-salt bath). *n*-BuMgCl or *i*-PrMgCl (0.5 mL, 2M solution) or PhMgCl (1 mL, 2M solution) was added via a syringe in one portion. The mixture was stirred at −20 °C for 10 min when *n*-BuMgCl or *i*-PrMgCl was used and 90 min with PhMgCl. Then the solution was quenched at −20 °C by the addition of electrophile via a syringe. Finally, the reaction mixture was poured into a saturated aq NH_4Cl solution (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL) and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a Silica Flash Cartridge applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 25 min, 25 mL/min).

As an example, the following compound was prepared according to this general procedure:

2-Benzyl-4-deutero-5-methoxypyridazin-3(2*H*)-one (2a). *n*-BuMgCl (1.8 mL, 3.60 mmol) and D_2O (0.2 mL, 11.6 mmol). The yield of **2a** is 95% (0.206 g); light-yellow needles. ^{1}H NMR ($CDCl_3$) δ: 7.79 (s, 1H), 7.41−7.36 (m, 2H), 7.34−7.27 (m, 3H), 5.27 (s, 2H), 4.26 (s, 3H). MP 93 °C. HRMS (ESI) for $C_{12}H_{11}DN_2O_2$ $[M + H]^+$, calcd 218.1040, found 218.1044. ^{13}C NMR ($CDCl_3$) δ: 161.8, 160.4, 136.6, 132.7, 128.6, 127.8, 103.2 (t, C-D, J = 25.52 Hz), 55.7, 54.3.

General Procedure 2 for the Tandem Functionalization of Pyridazin-3(2*H*)-ones via S_NAE and Bromine−Magnesium Exchange with RMgCl on 2-Benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one (4). Bromopyridazin-3(2*H*)-one **4** (0.295 g, 1 mmol) was brought in a 50 mL two-necked round-bottomed flask and put under argon atmosphere making use of a Schlenk apparatus. Subsequently 4 mL of THF was added and the solution was cooled to −20 °C (ice-salt bath). *n*-BuMgCl or *i*-PrMgCl (1,5 mL, 2*M* solution) or PhMgCl (2 mL, 2M solution) was added via a syringe in one portion. The mixture was stirred at −20 °C for 20 min when *n*-BuMgCl or *i*-PrMgCl was used and 90 min with PhMgCl. Then, the solution was quenched at −20 °C by the addition of electrophile via a syringe and stirred overnight (to ambient temperature). Finally, the reaction mixture was poured into a saturated aq NH_4Cl solution (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL) and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a Silica Flash Cartridges applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 25 min, 25 mL/min).

As an example, the following compound was prepared according to this general procedure:

2-Benzyl-5-[hydroxy(phenyl)methyl]-4-isopropylpyridazin-3(2*H*)-one (6b). Benzaldehyde (0.3 mL, 2.96 mmol). Compound **6b** was obtained in 76% (0.255 g) yield; yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.99 (s, 1H), 7.40−7.21 (m, 10H), 5.98 (d, 1H, J = 4.2 Hz), 5.28 (d, 1H, J = 14.1 Hz), 5.17 (d, 1H, J = 14.1 Hz), 3.14 (m, 2H, J = 6.9 Hz), 1.29 (d, 3H, J = 6.9 Hz), 1.11 (d, 3H, J = 6.9 Hz). HRMS (ESI) for $C_{21}H_{22}N_2O_2$ $[M + H]^+$, calcd 335.1760, found 335.1758. ^{13}C NMR ($CDCl_3$) δ: 159.5, 143.2, 141.4, 141.4, 136.5, 135.9, 128.9, 128.7, 128.5, 128.3, 127.7, 126.5, 70.2, 55.1, 28.5, 19.3, 18.5.

General Procedure 3 for the Functionalization of Pyridazin-3(2*H*)-ones via Regioselective Bromine−Magnesium Exchange with RMgCl on 2-Benzyl-4,5-dibromopyridazin-3(2*H*)-one (10). Bromopyridazin-3(2*H*)-one **10** (0.344 g, 1 mmol) was brought in a 50 mL two-necked round-bottomed flask and put under argon atmosphere making use of a Schlenk apparatus. Subsequently, 4 mL of THF was added and the solution was cooled down to −20 °C (ice-salt bath). *n*-BuMgCl (0.5 mL, 2M solution) was added via a syringe in one portion. The mixture was stirred at −20 °C for 3 min. Then the solution was quenched at −20 °C by the addition of electrophile via a syringe. Finally, the reaction mixture is poured into a saturated solution of aq NH_4Cl (10 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL) and subsequently dried over $MgSO_4$. The organic phase was evaporated to dryness under reduced pressure and the residue separated with an automated chromatography system using a Silica Flash Cartridges applying a heptane−ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 25 min, 25 mL/min).

As an example, the following compound was prepared according to this general procedure:

2-Benzyl-5-bromo-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (11d). DMF (0.23 mL, 3 mmol). The reaction mixture was stirred for 45 min, after which it was quenched with aq NH_4Cl. Compound **11d** was obtained in 78% (0.229 g) yield; yellow oil. ^{1}H NMR ($CDCl_3$) δ: 10.28 (s, 1H), 7.97 (s, 1H), 7.46−7.41 (m, 2H), 7.37−7.29 (m, 3H), 5.31 (s, 2H). HRMS (ESI) for $C_{12}H_9BrN_2O_2$ $[M + H]^+$, calcd 292.9926, found 292.9937. ^{13}C NMR ($CDCl_3$) δ: 158.6, 139.9, 143.8, 129.6, 129.0, 128.9, 128.6, 128.7, 128.5, 55.6.

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Supporting Information Available: Instrumentation and chemicals, experimental procedures and characterization data for all compounds, crystallographic information (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.