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# Synthesis of Functionalized Pyridazin-3(2*H*)-ones via Nucleophilic Substitution of Hydrogen ($S_NH$)

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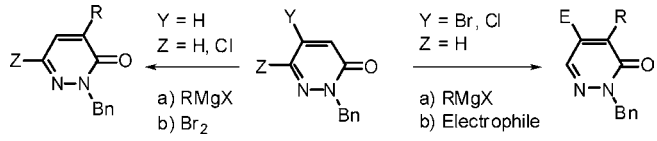
## ABSTRACT




**Reaction of 2-benzyl-5-halopyridazin-3(2*H*)-ones (3) with Grignard reagents followed by quenching with electrophiles unexpectedly yielded 4,5-disubstituted pyridazin-3(2*H*)-ones instead of 5-substituted pyridazin-3(2*H*)-ones. These reactions represent the first examples of cine substitution in which the anionic $\sigma^H$-adduct is quenched by electrophiles (other than a proton) before elimination takes place. Insight into the reaction mechanism led to the direct transformation of 2-benzylpyridazin-3(2*H*)-one (7) and 2-benzyl-6-chloropyridazin-3(2*H*)-one (9) into the corresponding C-4 alkyl and aryl derivatives (when $Br_2$ was used as the electrophile).**

A pyridazin-3(2*H*)-one core can be considered as a privileged scaffold in agrochemistry due to its presence in a remarkable number of launched pesticides (e.g., herbicides: Chloridazon, Norflurazon, Oxapyrazon, Flufenpyr, Dimidazon; fungicide: Diclomezine; insecticides: Pyridaphenthion, Pyridaben).[1] Remarkably, the number of available synthetic methods involving C-functionalizations of the pyridazin-3(2*H*)-one core is limited.[2] In an attempt to fill this gap our research group recently started to explore the reactivity of the pyridazin-3(2*H*)-one core toward Grignard reagents. In 2009 we described a bromine−magnesium exchange on bromopyridazin-3(2*H*)-ones followed by quenching with electrophiles.[3] While the intended functionalization was successfully achieved on 2-benzyl-4-bromo-5-methoxypyridazin-3(2*H*)-one, a different reactivity was observed with 2-benzyl-5-bromo-4-methoxypyridazin-3(2*H*)-one. An unexpected tandem reaction involving nucleophilic substitution via addition elimination ($S_NAE$) at C-4 and subsequent bromine−magnesium exchange at C-5 occurred. Quenching with electrophiles yielded 4,5-disubstituted pyridazin-3(2*H*)-ones with the R group of the RMgX reagent built in at C-4, and the electrophile at C-5.

To avoid the $S_NAE$ reaction, we decided to test 2-benzyl-5-bromopyridazin-3(2*H*)-one (**3a**) as substrate since it does not contain a leaving group at C-4. **3a** can be synthesized in a two-step procedure from commercially available 4,5-dibromopyridazin-3(2*H*)-one.[3] Surprisingly, reaction of **3a** with *n*-BuMgCl followed by quenching with $D_2O$ gave 2-benzyl-4-butyl-5-deuteropyridazin-3(2*H*)-one (**4a**) instead of the expected 2-benzyl-5-deuteropyridazin-3(2*H*)-one (Table 1). This is exactly the same reaction product as obtained when starting from 2-benzyl-5-bromo-4-methoxypyridazin-

(1) Unger, T. A. *Pesticide Synthesis Handbook*; Noyes: Park Ridge. NJ, 1996.

(2) For reviews dealing with the synthesis, functionalization, and application of pyridazines and pyridazin-3(2*H*)-ones see: (a) Kolar, P.; Tišler, M. *Adv. Heterocycl. Chem.* **1999**, *75*, 167. (b) Tapolcsányi, P.; Mátyus, P. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Societa Chimica Italiana: Rome, Italy, 2002; Vol. 6, p 369. (c) Haider, N., Holzer, W. In *Science of Synthesis*; Yamamoto, Y., Ed.; Thieme: New York, 2004; Vol. 16, p 125. (d) Maes, B. U. W.; Lemière, G. L. F. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Aitken, A., Eds.; Elsevier: New York, 2008; Vol. 8, p 1.

(3) Ryabtsova, O.; Verhelst, T.; Baeten, M.; Maes, B. U. W. *J. Org. Chem.* **2009**, *74*, 9440.

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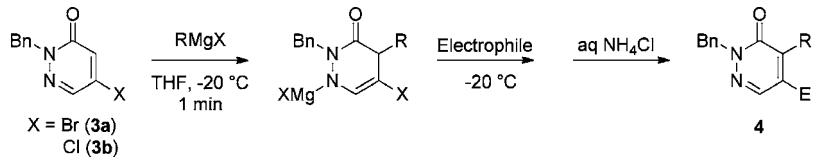
**Table 1.** Cine Substitution on 5-Halopyridazin-3(2*H*)-ones (**3**) Involving Electrophiles




X = Br (**3a**)
Cl (**3b**)

**4**

| entry | R | electrophile | E | **4** | yield (**3a**, X = Br) (%)[a] | yield (**3b**, X = Cl) (%)[b] |
|---|---|---|---|---|---|---|
| 1 | *n*-Bu | $D_2O$ | D | **4a** | 43 | 66 |
| 2 | *n*-Bu | PhCHO | PhCH(OH) | **4b** | 47 | 67 |
| 3 | *i*-Pr | PhCHO | PhCH(OH) | **4c** | 46 | 82 |
| 4 | Ph | PhCHO | PhCH(OH) | **4d** | 35[c] | 79[d] |
| 5 | *n*-Bu | PhCOCOOMe | PhC(OH)COOMe | **4e** | 14 | 69 |
| 6 | *i*-Pr | PhCOCOOMe | PhC(OH)COOMe | **4f** | 25 | 42 |
| 7 | Ph | PhCOCOOMe | PhC(OH)COOMe | **4g** | 38[c] | 75[d] |
| 8 | *n*-Bu | Furfural | $(C_4H_3O)$CHOH | **4h** | 62 | 67 |
| 9 | *i*-Pr | Furfural | $(C_4H_3O)$CHOH | **4i** | 60 | 76 |
| 10 | Ph | Furfural | $(C_4H_3O)$CHOH | **4j** | 38[c] | 61[d] |
| 11 | *n*-Bu | DMF | HCO | **4k** | 0 | 0 |
| 12 | *n*-Bu | MeSSMe | SMe | **4*l*** | 0 | 0 |
| 13 | *n*-Bu | $MeSO_2SMe$ | SMe | **4*l*** | | 83 |
| 14 | Ph | $MeSO_2SMe$ | SMe | **4m** | | 93[d] |
| 15 | *n*-Bu | $I_2$ | Cl | **4n** | 0 | 0 |
| 16 | *n*-Bu | ICl | Cl | **4n** | 0 | 40 |
| 17 | *n*-Bu | $Br_2$ | Cl | **4n** | | 58 |
| 18 | Ph | $Br_2$ | Cl | **4o** | | 22[d] |

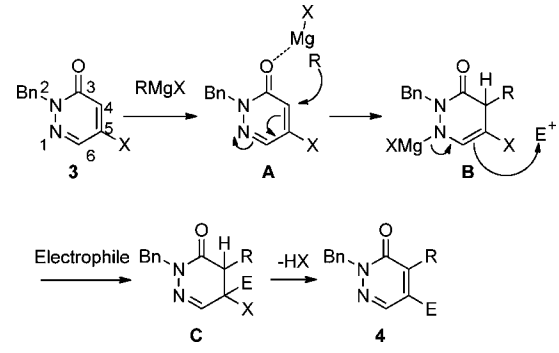
[a] **3a** (1 mmol), 0.5 mL of 2 M RMgCl (1 equiv), THF (4 mL), −20 °C, 1 min; electrophile (1.2 equiv); aq $NH_4Cl$. [b] **3b** (1 mmol), 0.65 mL of 2 M RMgCl (1.3 equiv), THF (4 mL), −20 °C, 1 min; electrophile (1.6 equiv); aq $NH_4Cl$. [c] **3a** (1 mmol), 1 mL of 2 M RMgCl (2 equiv), THF (4 mL), −20 °C, 1 min; electrophile (2.1 equiv); aq $NH_4Cl$. [d] **3b** (1 mmol), 1.30 mL of 2 M RMgCl (2.6 equiv), THF (4 mL), −20 °C, 1 min; electrophile (2.86 equiv); aq $NH_4Cl$.

3(2*H*)-one.[3] RMgX apparently still acts as a nucleophile even though no leaving group is present in C-4 and the electrophile is built in the C-5 position. MS analysis of the crude reaction mixture revealed that besides **4a**, also 2-benzyl-4-butylpyridazin-3(2*H*)-one and a product of which the molecular mass is consistent with 1′,2-dibenzyl-5′-butyl-4,4′-bipyridazine-3,6′(1′*H*,2*H*)-dione (**5**) were formed. To suppress the formation of these side products the reaction conditions were optimized. Using just 1 equiv of *n*-BuMgCl and a maximum reaction time of 1 min, before quenching with $D_2O$, maximized the yield of **4a** (Table 1, entry 1). Longer reaction times consistently led to the formation of undesired 2-benzyl-4-butylpyridazin-3(2*H*)-one and **5**. A variety of electrophiles were tested under the optimized conditions: benzaldehyde, methyl oxo(phenyl)acetate, and furfural gave the corresponding products (**4b**, **4e**, and **4h**) in moderate to good yields (Table 1, entries 2, 5, and 8). Interestingly, when DMF, $Me_2S_2$, and $I_2$ were used, no reaction product was formed (Table 1, entries 11, 12, and 15). Besides *n*-BuMgCl, two other organomagnesium reagents (*i*-PrMgCl and PhMgCl) were tested in combination with the same set of electrophiles. For *i*-PrMgCl the same reaction conditions were applied, which resulted in similar yields (Table 1, entries 3, 6, and 9). The less nucleophilic PhMgCl, however, required 2 equiv (Table 1, entries 4, 7, and 10).

As nucleophilicity of the RMgCl reagent seemed to play an important role we reasoned that a more electrophilic substrate such as 2-benzyl-5-chloropyridazin-3(2*H*)-one (**3b**) should give better yields. Chloropyridazinone **3b** can be obtained in a two-step synthesis starting from commercially available furfural.[4] To suppress the formation of **5** a larger amount of RMgCl was required for **3b** in comparison with analogous reactions on **3a**. Gratifyingly, significantly higher yields were indeed obtained (Table 1).

We believe that the carbonyl of the lactam function **3** coordinates the RMgX reagent (**A**) (Scheme 1). Hereby the

**Scheme 1.** Proposed Reaction Mechanism for Cine Substitution on 5-Halopyridazin-3(2*H*)-ones (**3**)



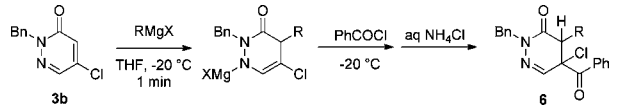

nucleophilicity of the Grignard reagent is increased as well as the electrophilicity of C-4, both favoring nucleophilic addition

(4) Hachihama, Y.; Shono, T.; Ikeda, S. *J. Org. Chem.* **1964**, *29*, 1371.

(5) The lactam function acts as a directing group for the nucleophilic addition reaction, which resembles a Directed Metallation Group (DMG) in Directed ortho Metallations (DoMs) with organometallic species. For a review dealing with directed metallation of diazines, see: Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489.

at C-4 of the pyridazin-3(2*H*)-one.[3,5] Moreover, the coordination creates a proximity effect of $R^-$ toward C-4 (intramolecular reaction). Nucleophilic addition is expected to occur easier on more electrophilic substrates, presumably explaining the differences observed between substrates **3a** and **3b**. Nucleophilic addition at C-4 yields the anionic $\sigma^H$-adduct **B**, which is inductively stabilized by the halogen atom at C-5 and resonance stabilized at N-1 (Scheme 1). Upon addition of electrophile a 5-substituted 4-alkyl (or 4-aryl)-2-benzyl-5-halo-4,5-dihydropyridazin-3(2*H*)-one (**C**) is formed, which subsequently eliminates HX yielding **4** (Scheme 1).[6] Remarkably, when benzoyl chloride was used as the electrophile no elimination occurs and 5-benzoyl-2-benzyl-4-alkyl-5-chloro-4,5-dihydropyridazin-3(2*H*)-ones (**6**) were isolated (Table 2). This supports our mechanistic hypothesis.

**Table 2.** Attempted Cine Substitution on 5-Chloropyridazin-3(2*H*)-one (**3b**) with Benzoyl Chloride as Electrophile[a]




| entry | R | electrophile | 6 | yield (%) |
|---|---|---|---|---|
| 1 | *n*-Bu | PhCOCl | **6a** | 37 |
| 2 | *i*-Pr | PhCOCl | **6b** | 60 |

[a] **3b** (1 mmol), 0.5 mL of 2 M RMgCl (1 equiv), THF (4 mL), −20 °C, 1 min; electrophile (1.5 equiv); aq $NH_4Cl$.

Mechanistically, the reaction is a cine-type substitution in which the anionic $\sigma^H$-adduct formed upon nucleophilic addition is quenched by electrophiles (other than a proton) before elimination takes place.[7,8] To the best of our knowledge no such cine nucleophilic substitutions of hydrogen have hitherto appeared in the literature. The resonance and inductive stabilization effects of the anionic species **B** explain why weaker electrophiles such as DMF, $Me_2S_2$, and $I_2$ cannot be used in our functionalization process (Table 1, entries 11, 12, and 15). This was further supported by an experiment in which MeSSMe was replaced by the more electrophilic $MeSSO_2Me$, smoothly yielding the desired pyridazin-3(2*H*)-one **4*l*** in 83% yield (Table 1, entry 13). A similar reaction involving PhMgCl as the nucleophile gave 2-benzyl-4-phenyl-5-methylthiopyridazin-3(2*H*)-one (**4m**) in a good yield (Table 1, entry 14). Analogously, when $I_2$ was replaced by ICl as reagent in a reaction with *n*-BuMgCl, 2-benzyl-4-butyl-5-chloropyridazin-3(2*H*)-one (**4n**) could be obtained (Table 1, entry 16). The use of more electrophilic $Br_2$ gave a higher yield of **4n** (Table 1, entry 17). Interestingly, no trace of 2-benzyl-4-butyl-5-iodopyridazin-3(2*H*)-one or 5-bromopyridazin-3(2*H*)-one was detected when using ICl or $Br_2$, respectively, as the electrophile. This can be rationalized in terms of better leaving group properties of iodine and bromine. Reaction of **3b** with PhMgCl and quenching with $Br_2$ gave 2-benzyl-5-chloro-4-phenylpyridazin-3(2*H*)-one (**4o**) (Table 1, entry 18). The 5-chloro-4-(alkyl or aryl)pyridazin-3(2*H*)-one compound class is very interesting as the C-5 chlorine allows further decoration of the pyridazinone core via $S_NAE$ and Pd-catalyzed cross-coupling reactions.[2,9,10] When alcohols are used as nucleophiles on 5-chloro-4-arylpyridazin-3(2*H*)-one substrates for instance, 5-alkoxy-4-arylpyridazin-3(2*H*)-ones are obtained. This pyridazin-3(2*H*)-one subclass possesses interesting biological properties such as the recently disclosed insecticidal activity against Myzus Persicae.[11] An example of a Pd-catalyzed cross-coupling reaction on 4-aryl-5-chloropyridazin-3(2*H*)-ones is a Suzuki reaction with arylboronic

(6) The elimination of HX from 5-substituted 4-alkyl (or 4-aryl)-2-benzyl-5-halo-4,5-dihydropyridazin-3(2*H*)-one (**C**) can occur before or after the addition of $NH_4Cl$.

(7) For reviews and a book dealing with nucleophilic aromatic substitution of hydrogen see: (a) Chupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: San Diego, CA, 1994. (b) Suwiński, J.; Œwierczek, K. *Tetrahedron* **2001**, *57*, 1639. (c) van der Plas, H. C. *Adv. Heterocycl. Chem.* **2004**, *86*, 1. (d) Mákosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631. (e) Gulevskaya, A. V.; Pozharskii, A. F. *Russ. Chem. Bull.* **2008**, *57*, 913. (f) Mákosza, M. *Chem. Soc. Rev.* **2010**, *39*, 2855.

(8) For cine substitutions in 5-bromo- and 5-chloropyridazine-3,6(1*H*,2*H*)-diones with O, S, and N nucleophiles yielding the corresponding 4-substituted pyridazine-3,6(1*H*,2*H*)-diones see: (a) Stam, C.; Zwinselman, J. J.; van der Plas, H. C.; Bałoniak, S. *J. Heterocycl. Chem.* **1979**, *16*, 855. (b) Bałoniak, S.; Ostrowicz, A. *Pol. J. Chem.* **1991**, *65*, 1085. (c) Bałoniak, S.; Ostrowicz, A. *Pol. J. Chem.* **1992**, *66*, 935. Cine substitutions in halopyridazin-3(2*H*)-ones have not been reported. Addition of Grignard reagents to pyridazine derivatives yielding substituted dihydropyridazines have been described. A separate reaction step is normally required for a full reoxidation to the pyridazine. For examples, see: (d) Tišler, M.; Stanovnik, B. In *Comprehensive Heterocyclic Chemistry I*; Katritzky, A. R., Rees, C. W., Boulton, A. J., McKillop, A., Eds.; Elsevier: New York, 1984; Vol. 3, p 1. (e) Coates, W. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Boulton, A. J., Eds.; Elsevier: New York, 1996; Vol. 6, p 1.

(9) For reviews dealing with Pd-catalyzed reactions on halopyridazines and halopyridazin-3(2*H*)-ones, see: (a) Maes, B. U. W.; Košmrlj, J.; Lemière, G. L. F. *J. Heterocycl. Chem.* **2002**, *39*, 535. (b) Maes, B. U. W.; Tapolcsányi, P.; Meyers, C.; Mátyus, P. *Curr. Org. Chem.* **2006**, *10*, 377. (c) 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.

(10) For selected examples of Pd-catalyzed reactions on halopyridazines and halopyridazin-3(2*H*)-ones, see: (a) Turck, A.; Plé, N.; Mojovic, L.; Quéguiner, G. *Bull. Soc. Chim. Fr.* **1993**, *130*, 488. (b) Trécourt, F.; Turck, A.; Plé, N.; Paris, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1995**, *32*, 1057. (c) Draper, T. L.; Bailey, T. R. *J. Org. Chem.* **1995**, *60*, 748. (d) Turck, A.; Plé, N.; Leprêtre-Gaquère, A.; Quéguiner, G. *Heterocycles* **1998**, *49*, 205. (e) Parrot, I.; Rival, Y.; Wermuth, C. G. *Synthesis* **1999**, 1163. (f) Maes, B. U. W.; R'kyek, O.; Košmrlj, J.; Lemière, G. L. F.; Esmans, E.; Rozenski, J.; Dommisse, R. A.; Haemers, A. *Tetrahedron* **2001**, *57*, 1323. (g) R'Kyek, O.; Maes, B. U. W.; Jonckers, T. H. M.; Lemière, G. L. F.; Dommisse, R. A. *Tetrahedron* **2001**, *57*, 10009. (h) Tapolcsányi, P.; Krajsovszky, G.; Andó, R.; Lipcsey, P.; Horváth, G.; Mátyus, P.; Riedl, Z.; Hajós, G.; Maes, B. U. W.; Lemière, G. L. F. *Tetrahedron* **2002**, *58*, 10137. (i) Parrot, I.; Ritter, G.; Wermuth, C. G.; Hibert, M. *Synlett* **2002**, 1123. (j) Sotelo, E.; Coelho, A.; Raviña, E. *Tetrahedron Lett.* **2003**, *44*, 4459. (k) Stevenson, T. M.; Crouse, B. A.; Thieu, T. V.; Gebreysus, C.; Finkelstein, B. L.; Sethuraman, M. R.; Dubas-Cordery, C. M.; Piotrowski, D. L. *J. Heterocycl. Chem.* **2005**, *42*, 427. (l) Johnston, K. A.; Allcock, R. W.; Jiang, Z.; Collier, I. D.; Blakli, H.; Rosair, G. M.; Bailey, P. D.; Morgan, K. M.; Kohno, Y.; Adams, D. R. *Org. Biomol. Chem.* **2008**, *6*, 175. (m) Clapham, K. M.; Batsanov, A. S.; Greenwood, R. D. R.; Bryce, M. R.; Smith, A. E.; Tarbit, B. *J. Org. Chem.* **2008**, *73*, 2176.

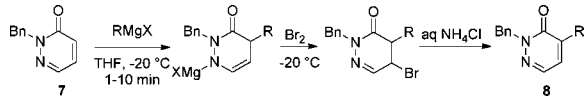
(11) Lehr, S.; Schenke, T.; Rosinger, C. H.; Fischer, R.; Haeuser-Hahn, I.; Feucht, D.; Dittgen, J.; Cristau, P.; Gaertzen, O.; Hermann, S.; Malsam, O.; Franken, E.-M. WO 2010078912 A1, 2010.

(12) (a) Li, C. S.; Brideau, C.; Chan, C. C.; Savoie, C.; Claveau, D.; Charleson, S.; Gordon, R.; Greig, G.; Gauthier, J. Y.; Lau, C. K.; Riendeau, D.; Thérien, M.; Wong, E.; Prasit, B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 597. (b) Li, C. S.; Prasit, P.; Gauthier, J. Y.; Lau, C. K.; Therien, M. WO Patent 9841511 A1, 1998; *Chem. Abstr.* **1998**, *129*, 275920.

acids yielding 4,5-diarylpyridazin-3(2*H*)-ones which are known as potent, selective, and orally active cyclooxygenase-2 inhibitors.[12]

In view of the reactivity of **3** with RMgX reagents we wondered whether 2-benzylpyridazin-3(2*H*)-one (**7**) would also undergo nucleophilic addition. When an electrophile, which can act as a leaving group (e.g., $Br_2$), would be used to quench the $\sigma^H$-adduct, elimination can still occur.[8] In this way C-unsubstituted pyridazin-3(2*H*)-one **7** could be directly transformed into 4-alkyl- and 4-aryl-2-benzylpyridazin-3(2*H*)-ones (**8**) without prior introduction of a leaving group in the pyridazin-3(2*H*)-one substrate. Mechanistically this is an oxidative nucleophilic substitution of hydrogen.[7] Gratifyingly, a test experiment with *n*-BuMgCl revealed that this approach indeed works when $Br_2$ is used as electrophile (Table 3, entry 1). 3 (R = alkyl) to 4 (R = aryl) equiv of RMgCl and 4 to 5 equiv of $Br_2$ were required. The use of $I_2$ instead of $Br_2$ gave very poor results, which is in agreement with the results obtained for **3b** (Table 1, compare entries 15 and 17). Besides butyl other alkyl groups, exemplified by isopropyl, could similarly be introduced when the corresponding RMgCl reagent was used (Table 3, entry 2). Interestingly, extension to C-4 arylation via reaction with ArMgCl nucleophiles is also possible (Table 3, entry 3). Subsequently, we decided to test the suitability of 2-benzyl-6-chloropyridazin-3(2*H*)-one (**9**) as substrate. This pyridazin-3(2*H*)-one is definitely more challenging as a competitive $S_NAE$ reaction at C-6 could occur. **9** can be easily synthesized in two steps starting from commercially available 3,6-dichloropyridazine.[10l] Interestingly, the alkylation and arylation procedure developed for **7** could be directly applied on **9** without any sign of $S_NAE$ at C-6 (Table 4).[13] The yields obtained starting from **9** were slightly higher than those with substrate **7**, presumably due to its increased electrophilic character. Reaction products **10** are very interesting synthetic intermediates as these compounds allow subsequent C-6 functionalization via $S_NAE$ or Pd-catalyzed cross-coupling reactions with organometallic reagents accessing 4,6-disubstituted pyridazin-3(2*H*)-ones, which are well-known for their interesting biological activities. 4,6-Diphenylpyridazin-3(2*H*)-one, for instance, is a precursor for the synthesis of Minozac (4,6-diphenyl-3-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridazine), which is a drug candidate for the treatment of Alzheimer disease.[14] The classical approach to prepare 4,6-disubstituted (alkyl, aryl) pyridazin-3(2*H*)-ones involves ring synthesis via condensation of an appropriately substituted 4-oxoalkanoic acid or ester with hydrazine derivatives.[8e]

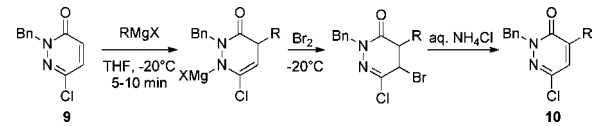
**Table 3.** Functionalization of Pyridazin-3(2*H*)-one **7** via Oxidative Nucleophilic Substitution of Hydrogen[a]




| entry | R | **8** | yield (%) |
|---|---|---|---|
| 1 | *n*-Bu | **8a** | 40 |
| 2 | *i*-Pr | **8b** | 53 |
| 3 | 4-MePh | **8c** | 27 |

[a] **7** (1 mmol), 2 M RMgCl (3−4 equiv), THF (4 mL), −20 °C, 1−10 min; $Br_2$ (4−5 equiv); aq $NH_4Cl$.

**Table 4.** Functionalization of Pyridazin-3(2*H*)-one **9** via Oxidative Nucleophilic Substitution of Hydrogen[a]




| entry | R | **10** | yield (%) |
|---|---|---|---|
| 1 | *n*-Bu | **10a** | 62 |
| 2 | *i*-Pr | **10b** | 60 |
| 3 | Ph | **10c** | 20 |
| 4 | 4-MePh | **10d** | 57 |
| 5 | 4-MeOPh | **10e** | 40 |
| 6 | 2-MeOPh | **10f** | 36 |
| 7 | 3,5-$Cl_2$Ph | **10g** | 83 |

[a] **9** (1 mmol), 2 M RMgCl (3−4 equiv), THF (4 mL), −20 °C, 5−10 min; $Br_2$ (4−5 equiv); aq $NH_4Cl$.

In conclusion, our results show that regioselective nucleophilic addition at C-4 of pyridazin-3(2*H*)-ones followed by quenching with electrophiles is an interesting and versatile new way to C-functionalize the pyridazin-3(2*H*)-one scaffold. When a leaving group is present at C-5, a double functionalization (C-4 and C-5) can be achieved in a single synthetic step. The absence of such a leaving group in combination with quenching with $Br_2$ as electrophile in situ places a leaving group at C-5, allowing C-4 mono functionalization. As a diverse set of groups can be easily introduced by using this $S_NH$ synthetic methodology, the identified protocols will allow the synthesis of a wide variety of new substituted pyridazin-3(2*H*)-ones (involving functional groups hitherto largely unexplored) with potential applications in agrochemistry as well as in pharmaceutical chemistry and material science.

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**Supporting Information Available:** Characterization data for all compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The coordination of the RMgX reagent to the carbonyl of the substrate presumably favors $\sigma^H$- over $\sigma^{Cl}$-adduct formation. For a discussion on the preferential formation of $\sigma^H$- over $\sigma^X$-adducts in electron deficient arenes, see ref 7f.

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