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Palladium-Catalyzed Chemoselective Monoarylation of Hydrazides for the Synthesis of [1,2,4]Triazolo[4,3-*a*]pyridines

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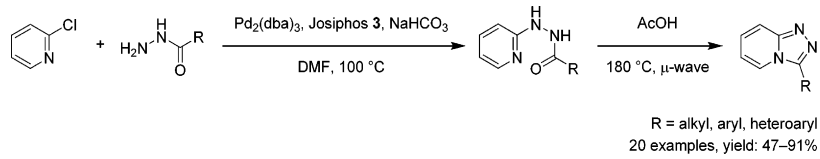
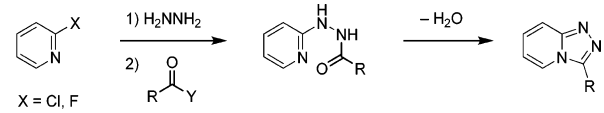
ABSTRACT



An efficient and convenient method for the synthesis of [1,2,4]triazolo[4,3-*a*]pyridines was exemplified by the synthesis of 20 analogues bearing a variety of substituents at the 3-position. The methodology involves a palladium-catalyzed addition of hydrazides to 2-chloropyridine, which occurs chemoselectively at the terminal nitrogen atom of the hydrazide, followed by dehydration in acetic acid under microwave irradiation.

Triazolopyridines represent an important class of heteroaromatic compounds. The [1,2,4]triazolo[4,3-*a*] pyridine moiety can be found in a variety of biologically active compounds, including antibacterial, antithrombotic, antiinflammatory, antiproliferative, and herbicidal agents.[1] Besides the oxidative cyclization of 2-pyridylhydrazones, the addition of hydrazine to pyridines bearing a leaving group in the 2-position followed by acylation and dehydration under a variety of conditions is the most commonly used method for the synthesis of [1,2,4]triazolo[4,3-*a*]pyridines (Scheme 1).[2]

Scheme 1. General Synthesis of [1,2,4]Triazolo[4,3-*a*]pyridines



In the course of our studies, we became interested in a general and convenient method for the synthesis of 3-substituted [1,2,4]triazolo[4,3-*a*]pyridines with a chemical handle at the 7-position suited for further elaboration. Although 4-bromo-2-fluoropyridine or 4-bromo-2-chloropyridine would be suitable starting materials, these compounds are relatively expensive. We envisioned that addition of hydrazides to a more economical starting material, 2,4-chloropyridine, followed by dehydration would provide a concise route to 3-substituted 7-chloro[1,2,4]triazolo[4,3-*a*]pyridines. However, it is documented that under thermal conditions nitrogen nucleophiles including hydrazine add selectively to the 4-position of the pyridine.[3]

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(1) For example, see: (a) Yoshimura, Y.; Tomimatsu, K.; Nishimura, T.; Miyake, A.; Hashimoto, N. *J. Antibiot.* **1992**, *45*, 721. (b) Sadana, A. K.; Mirza, Y.; Aneja, K. R.; Prakash, O. *Eur. J. Med. Chem.* **2003**, *38*, 533. (c) Lawson, E. C.; Hoekstra, W. J.; Addo, M. F.; Andrade-Gordon, P.; Damiano, B. P.; Kauffman, J. A.; Mitchell, J. A.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2619. (d) Kalgutkar, A. S.; Hatch, H. L.; Kosea, F.; Nguyen, H. T.; Choo, E. F.; McClure, K. F.; Taylor, T. J.; Henne, K. R.; Kuperman, A. V.; Dombroski, M. A.; Letavic, M. A. *Biopharm. Drug Dispos.* **2006**, *27*, 371. (e) Luethy, C.; Hall, R. G.; Edmunds, A.; Riley, S.; Diggelmann, M. *PCT Int. Appl. WO08006540*, 2008. (f) Abel, U.; Deppe, H.; Feurer, A.; Grädler, U.; Ott, I.; Matassa, V. G. *PCT Int. Appl. WO06058752*, 2006.

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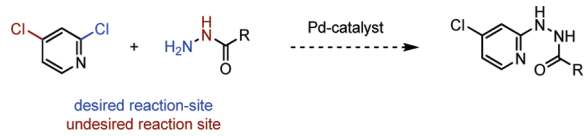
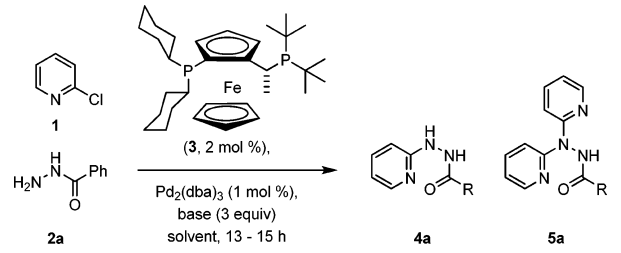
We decided to investigate the use of a transition metal catalyst to alter the selectivity in reactions of 2,4-dichloropyrdine with hydrazine derivatives (Scheme 2). A report by Abad et al. describing the regioselective palladium-catalyzed addition of ureas to 2,4-dichloropyridine at the 2-position suggested that the desired selectivity could be obtained.[4] A survey of the literature revealed that transition-metal-catalyzed additions of acylhydrazines to aromatic and heteroaromatic systems were indeed documented; in particular, *tert*-butylcarbazate ($BocHNNH_2$) is often used as the nucleophile. However, under palladium or copper catalysis the acylhydrazines react preferentially at the internal amide nitrogen atom rather than the terminal amine nitrogen atom.[5−7] This selectivity can be altered to the terminal nitrogen by introduction of sterically demanding groups on the electrophile.[5a,6b] Only one example is documented, in which the terminal nitrogen of benzoic hydrazide adds to a sterically unbiased aryliodide under copper catalysis.[6a] Therefore, at the outset of our studies, it was unclear if selectivity at the nucleophilic and electrophilic partner could be achieved (Scheme 2).

Scheme 2. Desired Regioselectivity



We first set out to find an appropriate palladium-based catalyst system that would provide good conversions as well as preferential monoarylation of the terminal nitrogen atom of benzoic hydrazide in a model reaction with 2-chloropyridine (**1**, Table 1).[8] Toward this end, **1** was subjected to 1 equiv of benzoic hydrazide (**2a**) at 100 °C in DMF in the presence of $Pd_2(dba)_3$ (1 mol %) and a diverse array of phosphine ligands (Josiphos **3**, Xant-Phos, BINAP, DPE, X-Phos, S-Phos, Q-Phos, DPPF, DtBPF, 2 mol % each).[9] Complete conversion was observed only in the reaction employing Josiphos **3** as the ligand, whereas all other catalyst systems led to incomplete conversion (<60%) of 2-chloropyridine to the monocoupled product **4a**.[10,11] The corresponding reaction in the absence of catalyst and ligand resulted in low conversion to the monoarylated product **4a** (entry 1).

Table 1. Reaction Optimizations[a]



entry	solvent	base	conversion[b]	[**4a**]/[**5a**][c]
1[d]	DMF	Cs_2CO_3	27	>100
2	DMF	Cs_2CO_3	>99	5.3
3	toluene	Cs_2CO_3	>99	0.1
4	toluene	K_3PO_4	>99	1.5
5	toluene	NaO*t*Bu	>99	2.3
6[e]	DME	NaO*t*Bu	>99	1.6
7[f]	DMF	Cs_2CO_3	>99	6.3
8[f]	DMF	K_2CO_3	>99	1
9[f]	DMF	Na_2CO_3	90	22
10[f]	DMF	$KHCO_3$	>99	11
11[f]	DMF	$NaHCO_3$	95	24
12[g]	DMF	$NaHCO_3$	>99	25
13[h]	DMF	$NaHCO_3$	94	16

[a] Unless otherwise specified, the reactions were performed at 100 °C using 1 equiv of **2a**. [b] HPLC conversion (215 nm) to product **4a** based on **1**. [c] Selectivity of **4a** vs **5a** determined by HPLC. [d] No catalyst added. [e] Reaction at 80 °C. [f] Using 1.3 equiv of **2a**. [g] Using 1.5 equiv of **2a**. [h] Using 1.5 equiv of **2a** and reduced catalyst and ligand loading (1 mol % Pd, 1 mol % ligand).

Regioisomeric products resulting from the nucleophilic attack of the internal nitrogen atom of the hydrazide were not detected under the conditions described above, but a significant amount of the bis-arylated product **5a** (15% by HPLC) was formed (entry 2). The formation of this by-product was even more pronounced when toluene or DME were used as solvents in the presence of cesium carbonate, sodium *tert*-butoxide, or potassium phosphate (entries 3−6) suggesting a significant role of the base in the reaction. In the screen of alternative carbonate bases using 1.3 equiv of

(2) (a) Sliskovic, D. R. Bicyclic 5−6 Systems with One Ring Junction Nitrogen Atom: Two Extra Heteroatoms 2: 0. In *Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982−1995: The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, New York, 1996; Vol. 8, Chapter 13, pp 367−388. (b) Jones, G. *Adv. Heterocycl. Chem.* **2002**, *83*, 1, and references cited therein.

(3) Schlosser, M.; Bobbio, C.; Rausis, T. *J. Org. Chem.* **2005**, *70*, 2494.

(4) Abad, A.; Agulló, C.; Cuñat, A. C.; Vilanova, C. *Synthesis* **2005**, 915.

(5) Palladium-catalyzed additions:(a) Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543. (b) Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351. (c) Lim, Y.-K.; Jung, J.-W.; Lee, H.; Cho, C.-G. *J. Org. Chem.* **2004**, *69*, 5778.

(6) Copper-catalyzed additions: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803. (c) Lavecchia, G.; Berteina-Raboin, S.; Guillaumet, G. *Tetrahedron Lett.* **2004**, *45*, 2389.

(7) A selective monoarylation of the terminal nitrogen atom of hydrazides with organobismuth reagents was reported: Tšubrik, O.; Mäeorg, U.; Sillard, R.; Ragnarsson, U. *Tetrahedron* **2004**, *60*, 8363.

(8) Exploration of copper-based catalyst systems was not within the scope of this investigation.

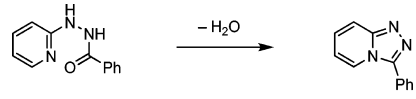
(9) Table 1 only contains a selected array of the conditions screened. All ligands were investigated in the presence of potassium phosphate (toluene), cesium carbonate (toluene, DMF), and sodium *tert*-butoxide (toluene, DME).

(10) The structure of **4a** was confirmed by NMR and by conversion to the corresponding triazolopyridine **6a**. Conversions were determined by HPLC (215 nm).

(11) For a leading reference regarding use of **3** for palladium-catalyzed couplings: Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371.

benzoic hydrazide, an increase in selectivity in the following order was observed: $K_2CO_3 < Cs_2CO_3 < KHCO_3 < Na_2CO_3 < NaHCO_3$ (entries 7−11). A further increase of excess benzoic hydrazide (1.5 equiv) allowed complete conversions using 2 mol % of palladium and ligand and allowed for excellent selectivity toward the desired product **4a** (entry 12). Since the reaction did not proceed to complete conversion using 1 mol % of catalyst (entry 13), the optimized conditions can be summarized as follows: 1.5 equiv of **2a**, 3 equiv of $NaHCO_3$, 2 mol % of Josiphos, and 1 mol % of $Pd_2(dba)_3$ in DMF at 100 °C.

Scheme 3. Dehydrative Cyclization



4a **6a**

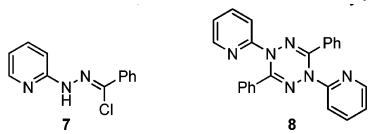
Having established optimized conditions for the palladium-catalyzed coupling reaction, conditions for the dehydrative cyclization were explored with substrate **4a** (Scheme 3). Use of phosphorus oxychloride (neat or in selected solvents such as toluene, acetonitrile, or chlorobenzene) at elevated temperatures (90−110 °C) led to formation of the desired product **6a**. However, these conditions were accompanied by formation of an impurity in varying levels (1−3% by HPLC),[12] which prompted us to turn our attention to alternative dehydration conditions. Thermal cyclization (110 °C) of **4a** in the presence of polyphosphoric acid[13] led to a clean conversion after 15 h, and the product **6a** could be isolated in 82% yield. To decrease reaction times, we explored other dehydrating conditions, including Dean−Stark conditions, molecular sieves, and orthoesters. In the event, we found that heating a solution of the addition product in glacial acetic acid in a microwave reactor to 180 °C provided quantitative formation of the triazolopyridine.[14] These conditions proved successful in cyclizing the crude product of the addition reaction, which was simply filtered through a plug of silica gel and hence offered a high-yielding and operationally very convenient method for the synthesis of [1,2,4]triazolo[4,3-*a*]pyridines.

Application of the optimized conditions to the reaction of 2,4-dichloropyridine with arylhydrazides was next attempted. The 2- vs 4-selectivity in the crude reaction mixture at the end of the coupling reaction was ∼6:1 (by HPLC), and exclusive attack at the terminal nitrogen of the hydrazide was observed. A product incorporating two hydrazine moieties on a pyridine ring was also detected by LC/MS. Overall, relatively disappointing assay yields (30−50%) were obtained, thereby hampering isolation of the coupled product. The relatively low yield can be explained due to oligomerization reactions of the primary products since the starting materials contain two potential electrophilic and three nucleophilic sites. A similar screen of catalysts and conditions as for 2-chloropyridine was conducted for 2,4-dichloropyridine. While it was successful in identifying alternative reaction conditions (DPPF, potassium phosphate, toluene) that led to higher conversions, it failed to significantly improve assay yields for the desired product.

We recognized that the novel reactivity in the palladium-catalyzed coupling of hydrazides would nonetheless offer a practical approach to a broad array of triazolopyridines. This methodology is particularly suitable for diversified lead-generation since a broad array of acyl hydrazides are commercially available.[15] Employing the optimized conditions,[16] a variety of 3-aryl-substituted triazolopyridines were synthesized (Table 2). The palladium-catalyzed addition of benzoic hydrazides bearing electron-donating groups (methyl, methoxy, hydroxyl) and of cinnamic hydrazide proceeded smoothly using 2 mol % of catalyst, whereas 5 mol % of catalyst was used for the reaction of electron-withdrawing substituted benzoic hydrazides (fluoro, chloro, difluoro, trifluoromethyl, carboxamido) to keep the reaction time at a convenient duration (13−15 h). The reaction conditions are also compatible with the use of heteroaromatic hydrazides, even though the corresponding triazolopyridines were isolated in somewhat lower yields (entries 12−16).

In the synthesis of **6h**, the addition of 4-carbamoylbenzoic hydrazide to 2-chloropyridine (entry 8) occurred selectively at the terminal nitrogen of the hydrazide, demonstrating the compatibility of amides with this methodology. On the other hand, the reaction of 4-aminobenzoic hydrazide with **1** under the standard conditions led to the formation of a mixture (ca. 1:1) of the desired addition product and another compound that incorporated one pyridine moiety on the hydrazide as well as one on the aniline nitrogen. We reached the steric limitation of our methodology in the synthesis of the 3-mesityl-substituted triazolopyridine **6k** (entry 11). The

(12) This impurity was tentatively assigned as structure **8** based on LC/MS data. The formation of this impurity is most likely caused by dimerization of intermediate **7**, which can be observed by LC/MS.



7 **8**

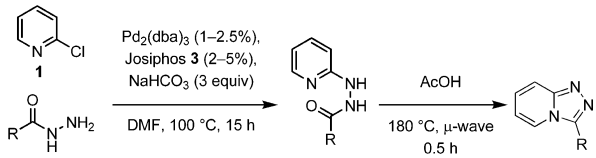
(13) Hansen, K. B.; Balsells, J.; Dreher, S.; Hsiao, Y.; Kubryk, M.; Palucki, M.; Rivero, N.; Steinhuebel, D.; Armstrong, J. D., III; Askin, D.; Grabowski, E. J. *Org. Process Res. Dev.* **2005**, *9*, 634.

(14) While this manuscript was in preparation, a method for the formation of [1,2,4]triazolo[4,3-*b*]pyridazines featuring microwave-assisted dehydration in acidic medium was published: Aldrich, L. N.; Lebois, E. P.; Lewis, L. M.; Nalywajko, N. T.; Niswender, C. M.; Weaver, C. D.; Conn, P. J.; Lindsley, C. W. *Tetrahedron Lett.* **2009**, *50*, 212.

(15) >3000 according to ACD.

(16) **General Experimental Procedure:** Neat 2-chloropyridine (2 mmol) was added to a mixture of hydrazide (3 mmol), $Pd_2(dba)_3$ (20−50 μmol), **3** (40−100 μmol), and $NaHCO_3$ (6 mmol) in DMF (4 mL), and the mixture was heated in a sealed vial at 100 °C for 15 h. The mixture was cooled to rt and filtered through a plug of silica gel (ca. 5 g), which was washed with *i*-PrOH/CH_2Cl_2 (1:9, 30 mL). The combined filtrates were concentrated under reduced pressure to deliver a brown oil that was taken on without further purification. A solution of this brown oil in glacial acetic acid (10 mL) was heated in a microwave reactor at 180 °C for 0.5 h. The mixture was cooled to rt and concentrated under reduced pressure, and the residue was partitioned between CH_2Cl_2 (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting black oil was purified by flash chromatography to deliver the desired product (see Supporting Information).

Table 2. Synthesis of 3-Substituted Triazolopyridines



entry	R	yield[a,b]	entry	R	yield[a,b]
1	**a**	91%	2	**b**	86%
3	**c**	71%	4	**d**	57%
5	**e**	82%	6	**f**	80%
7	**g**	69%	8	**h**	47%
9	**i**	74%	10	**j**	87%
11	**k**	80%[c]	12	**l**	64%
13	**m**	78%	14	**n**	69%
15	**o**	62%[d]	16	**p**	55%
17	Me **q**	89%[d]	18	*i*-Pr **r**	87%[d]
19	*t*-Bu **s**	91%[d]	20	**t**	90%[c]

[a] All products are characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. [b] Isolated yield. [c] See text. [d] The reaction required 60 h for complete conversion.

addition of 2,4,6-trimethylbenzoic hydrazide to 2-chloropyridine proceeded cleanly using 5% catalyst for 30 h at 100 °C; however, dehydration attempts in AcOH at 180 °C under microwave irradiation delivered no product, whereas acetylated **4k** was the major product at 200 °C. However, alternative dehydration conditions (5 equiv of $POCl_3$, chlorobenzene, 110 °C) delivered **6k** in 80% overall yield.

This methodology was also applicable to the synthesis of 3-alkyl and 3-alkenyl substituted triazolopyridines (Table 2, entries 17−20). Alkyl hydrazides proved to be less reactive substrates in the addition reaction with 2-chloropyridine, and more forcing conditions (5 mol % of catalyst, 60 h at 100 °C) had to be employed. Interestingly, in the first attempt toward the synthesis of the cinnamyl analogue (**6t**, entry 20), we isolated the desired product in only 60% yield together with 30% of the saturated analogue. Subjection of **6t** to the dehydration conditions (AcOH, 180 °C, microwave) did not generate this saturated product, neither in the absence nor presence of catalyst. The formal hydrogen necessary for the reduction was suspected to arise from an excess of hydrazide, but also addition of hydrazide with or without catalyst in these studies failed to provide any saturated product. Toward this end, we found that heating **6t** in AcOH in the presence of DMF (the solvent in the addition reaction) and Pd catalyst indeed produced the saturated undesired side product. Hence, the synthesis of **6t** included a chromatographic purification of the intermediate addition product, and the desired unsaturated triazolopyridine was obtained in 90% yield over the two steps.

In summary, we have developed an efficient procedure for the palladium-catalyzed addition of hydrazides to chloropyridines, which occurs selectively at the terminal nitrogen atom of the hydrazide. The products of this reaction were found to undergo dehydrative cyclizations upon heating in acetic acid under microwave irradiation. It was found that the crude products of the palladium-catalyzed addition reaction cleanly cyclized under these conditions making this reaction sequence an operationally very convenient and high-yielding method for the synthesis of [1,2,4]triazolo[4,3-*a*]pyridines.

Acknowledgment. We thank Dr. Andrew S. Tasker (Amgen, Inc.) for his support of this project as well as Prof. Stephen L. Buchwald (Massachusetts Institute of Technology) for insightful discussions.

Supporting Information Available: Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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