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Use of N-Protected Amino Acids in the Minisci Radical Alkylation

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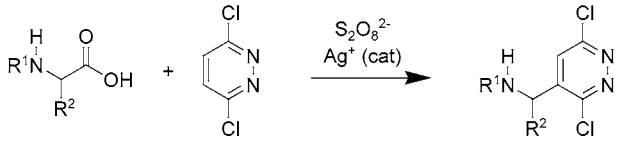
ABSTRACT

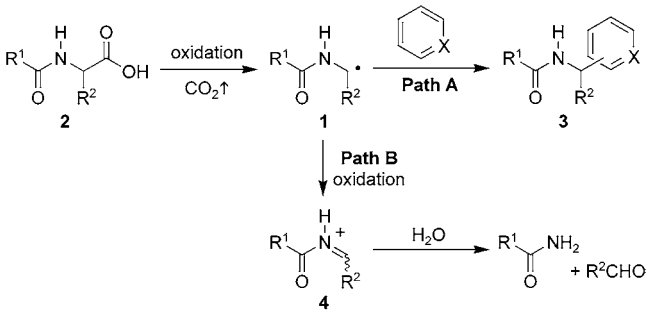


The Minisci radical alkylation has been demonstrated on a range of commercially available glycine derivatives and proceeds in good to high yield. When extending the reaction to other amino acids, competitive oxidation of the initially formed radical was overcome by using the phthalimide protecting group.

The selective functionalization of aromatic heterocycles is of paramount importance to the pharmaceutical industry in its quest for new drugs. Methods such as directed ortho metalation, nucleophilic addition, and Friedel−Crafts reactions are well accepted. The Minisci radical alkylation reaction offers a unique and complementary means of functionalizing electron-deficient aromatic heterocycles.[1] Nucleophilic addition of an alkyl radical to a protonated heterocycle followed by re-aromatization can allow carbon alkylation. Despite its apparent utility, few synthetically useful examples have been reported. We were interested in this reaction and the use of 1-amidoalkyl radical additions, in particular. Minisci has previously described peroxide-mediated hydrogen abstraction from DMF, and in this case, a mixture of acyl and 1-amidoalkyl addition products was obtained.[2] 1-Amidoalkyl radicals derived from tertiary amides have also shown use in the synthesis of nicotine[3] and folic acid[4] analogues. However, these reports are few and the use of secondary amides appears absent. In this paper, we extend the scope of the Minisci reaction by demonstrating that a range of readily available 1-amidoalkyl radicals afford alkylation products in good to high yields. Notably, secondary amides are shown to be compatible with this reaction.

As shown in Scheme 1, we planned to generate 1-amidoalkyl radicals **1** by the decarboxylation of protected α-amino acids **2** using catalytic silver with stoichiometric persulfate ($Ag^+/S_2O_8^{2-}$).[5] Radical **1** should then be captured by an electron-deficient heterocycle to afford amide **3** (path A, Scheme 1). The potential problem with this route is that oxidation of the radical to give imine **4** is expected to be a

Scheme 1



(1) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489. Minisci, F.; Recupero, F.; Punta, C.; Gambarotti, C.; Antonietti, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, 2496 and references therein.

(2) Gardini, G. P.; Minisci, F.; Palla, G.; Arnone, A.; Galli, R. *Tetrahedron Lett.* **1971**, 59.

(3) Heinisch, G.; Jentzsch, A.; Kirchner, I. *Tetrahedron Lett.* **1978**, 619.

(4) Tada, M.; Furuse, R.; Kashima, H. *Heterocycles* **1992**, *34*, 357.

(5) Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27.

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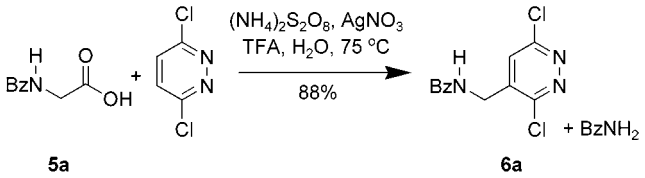
facile process (path B). In fact, this method of amidoalkyl radical oxidation is especially favored with an α-hetero substituent and is synthetically useful.[6] Another obstacle would be the possible instability of the product secondary amides **3** to the strongly oxidizing reaction conditions. The peroxydisulfate ion ($S_2O_8^{2-}$) is one of the strongest oxidizing agents (2.01 V standard reduction potential in aqueous solution),[5] and $K_2S_2O_8$ has been shown to dealkylate both secondary and tertiary amides under similar reaction conditions.[7]

Our study began using hippuric acid (*N*-benzoylglycine, **5a**) as radical source and 3,6-dichloropyridazine as the representative heterocycle (Scheme 2). Under optimized conditions, addition of an aqueous solution of ammonium persulfate (1.8 equiv) to a well-stirred mixture of hippuric acid (1.7 equiv), silver nitrate (10 mol %), trifluoroacetic acid (TFA, 20 mol %), and the pyridazine in water afforded the desired adduct **6a** in 88% yield. Small amounts of benzamide were observed which likely resulted from competitive oxidation of the radical (path B, Scheme 1). The high yield in this example indicated that the product was stable to the reaction conditions. We chose to use TFA instead of the typical sulfuric acid as it should lead to a milder reaction although sulfuric acid gave a similar yield. No products from decarboxylation of TFA were observed. Interestingly, when a syringe pump rather than a glass dropping funnel was used for the addition of the persulfate solution, a lower yield was obtained (55%). It has been noted that aqueous solutions of persulfate are unstable at room temperature and a metal syringe needle may accelerate this process.[8]

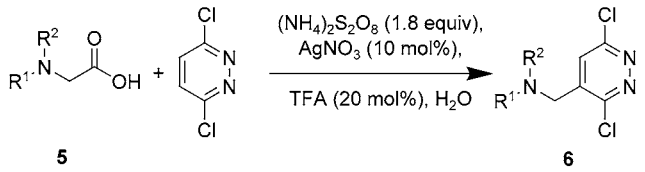
Scheme 2



5a **6a**

This reaction was simple to run and appeared synthetically useful, so its compatibility with other nitrogen protecting groups was assessed. As can be seen from Table 1, the reaction tolerated a range of commercially available glycine derivatives. The isolated yield for BzGlyOH, CbzGlyOH, TsGlyOH, and PhtGlyOH were all high (77−88%). The success of the Cbz group was somewhat surprising as hydrogen abstraction by either an inter- or intramolecular process to afford a benzylic radical could compete with the desired addition. The Boc derivative **5e** gave a lower yield due to deprotection under the reaction conditions. In this case, TFA was not added, which also resulted in a slower reaction. Double addition to the pyridazine is usually observed at <5%, however with acetylglycine (**5f**), up to 20% was observed which partly accounts for the lower yield. We also hoped to couple dipeptide **5g** however none of the desired product was isolated, possibly due to the low solubility of the starting material in water. The tertiary amide **5h** gave the expected product in good yield (79%). In most of these examples, unreacted 3,6-dichloropyridazine still remained so yields based on the pyridazine could be improved so long as dialkylation did not become a serious competing process.[9]

Table 1. Minisci Coupling of Commercial Glycine Derivatives



5 **6**

substrate	R^1	R^2	yield[a] (%)
5a	Bz	H	88
5b	Cbz	H	81
5c	Ts	H	77
5d	phthaloyl		81
5e	Boc	H	55[b]
5f	Ac	H	48
5g	BzGly	H	0
5h	Bz	Me	79

[a] Isolated yield. [b] No TFA was used.

We were interested in applying this chemistry to the regiocontrolled addition of unsymmetrically substituted pyridazines (Table 2).[10] Previous work had shown the addition of simple alkyl radicals to substrates **7a** and **7b** (X = Me and Ph, respectively) proceeded regioselectively.[11] In line with those results, the addition of the amidomethyl radical was highly selective leading to products **8a** and **8b** with the newly introduced group adjacent to the chlorine substituent. The radical alkylation of alkoxy pyridazines has not been assessed previously so substrates **7c** and **7d** were prepared. The addition to 3-chloro-6-methoxypyridazine (**7c**) also proceeded selectively, and it was a surprise that the addition was now opposite the previous examples with compound

(6) Chao, W.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 9199. Renaud, P.; Seebach, D. *Synthesis* **1986**, 424. For a review of 1-amidoalkyl radicals, see: Renaud, P.; Giraud, L. *Synthesis* **1996**, 913.

(7) Needles, H. L.; Whitfield, R. E. *J. Org. Chem.* **1964**, *29*, 3632.

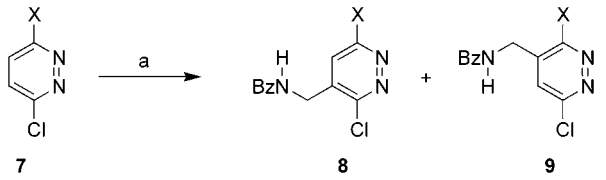
(8) Behrman, E. J.; Edwards, J. O. *Rev. Inorg. Chem.* **1980**, *2*, 179.

(9) **Representative Experimental Procedure.** A 500 mL round-bottom flask equipped with condenser, dropping funnel, nitrogen inlet and a Teflon-coated stir bar was charged with hippuric acid (10.2 g, 56.9 mmol), 3,6-dichloropyridazine (5.0 g, 33.6 mmol), $AgNO_3$ (0.57 g, 3.4 mmol), water (60 mL) and TFA (0.77 g, 6.7 mmol). The reaction mixture was warmed to 70 °C internal, and a solution of $(NH_4)_2S_2O_8$ (13.8 g, 60.5 mmol) in water (20 mL) was added over 20 min during which time CO_2 evolution and a small exotherm (10 °C rise) took place. After a 30 min age, isopropyl acetate (IPAc) (200 mL) was added and the reaction cooled to 20 °C. NH_4OH was added until the aqueous layer was pH 9, and then the layers separated. The aqueous layer was further extracted with IPAc (50 mL), and the combined organics were washed with $NaHCO_3$ (50 mL of 1 M aq solution), dried ($MgSO_4$), and filtered through a glass fiber disk, and product **6a** (8.32 g, 88%) was then isolated by crystallization from IPAc/hexanes.

(10) Functionalized pyridazines have been used in the synthesis of trisubstituted 1,2,4-triazolo[4, 3-*b*]pyridazines, a heterocyclic system common to a number of subtype selective GABA-A agonists; see: Collins, I.; Castro, J. L.; Street, L. J. *Tetrahedron Lett.* **2000**, *41*, 781. Sparey, T. J.; Harrison, T. *Tetrahedron Lett.* **1998**, *39*, 5873. Chloropyridazines are also useful as interleukin-1β converting enzyme inhibitors, see: Dolle, R. E.; Hoyer, D.; Rinker, J. M.; Morgan, T.; Schmidt, S. J.; Helaszek, C. T.; Ator, M. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1003.

(11) Samaritoni, J. G.; Babbitt, G. *J. Heterocycl. Chem.* **1991**, *28*, 583.

Table 2. Minisci Addition to Unsymmetric Pyridazines



7 8 9

substrate	X	**8**/**9**[b]	yield (%)
7a	Me	90:10	53[c]
7b	Ph	95:5	78[c]
7c	OMe	17:83	69[c]
7d	O*i*-Pr	24:76	84[d]

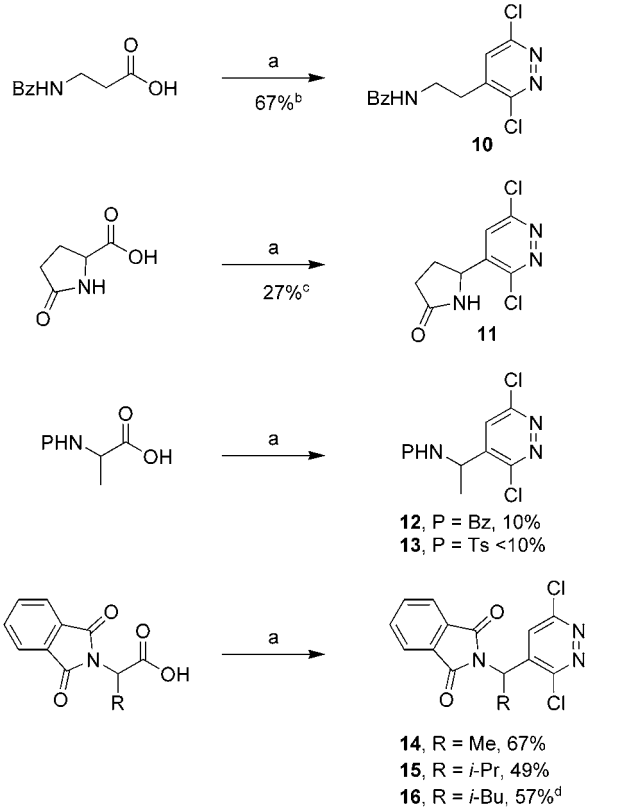
[a] Hippuric acid, $(NH_4)_2S_2O_8$, $AgNO_3$, TFA, H_2O, 75 °C. [b] Ratio determined by HPLC analysis at end of reaction. [c] Isolated yield of major component. [d] Combined yield of isomers.

9c predominating. When using the isopropoxy-substituted pyridazine **7d**, the selectivity was reduced but still in favor of the unexpected product **9d**. It appears the preferred site of attack for the nucleophilic alkyl radical is adjacent to the more electron withdrawing substituent (electronegativities of oxygen and chlorine are 3.44 and 3.16, respectively).[12]

The application of this methodology to amino acids other than glycine derivatives was then pursued (Scheme 3). The use of *N*-benzoyl-*β*-alanine gave the expected adduct **10** in good yield, and no benzamide was observed. This result shows that the amide group does not need to be directly adjacent to the radical for a successful coupling reaction. Unfortunately, using 2-pyrrolidinone-5-carboxylic acid the addition proceeded with low conversion to adduct **11,** and 6 equiv of reagent was required for a 27% yield with starting dichloropyridazine still present. Similarly, *N*-benzoylalanine gave a low yield of compound **12**, and a large amount of benzamide was present indicating that the oxidation of the alkyl radical (path B, Scheme 1) competed with addition to the heterocycle. The use of tosyl-protected alanine was no better with only a trace of product **13** observed.[13] Fortunately, changing to the phthalimide group gave improved results and starting with phthaloyl-protected alanine, a 67% yield of compound **14** was obtained. With this success, the commercially available valine and leucine derivatives were tried and gave the desired adducts, **15** and **16** respectively, in reasonable yield.

In conclusion, a general method for the addition of 1-amidoalkyl radicals derived from N-protected glycine derivatives to a representative electron deficient heterocycle is reported. The reaction afforded good to high yields of the desired Minisci adducts which were stable under the reaction conditions. The addition to unsymmetrical 3-alkoxy-6-chloropyridazines proceeded with surprising selectivity in favor of the 4-alkylated product. When extending this reaction to other amino acids derivatives, competing oxidation of the initially formed radical was observed. Nevertheless, when using the phthalimide protecting group, reasonable yields of the Minisci adducts were obtained.

Scheme 3 [a]



[a] Key: (a) 3,6-dichloropyridazine (1.0 equiv), amino acid (3 equiv), $(NH_4)_2S_2O_8$ (3.2 equiv), $AgNO_3$ (10 mol %), TFA (20 mol %), H_2O, 75 °C; (b) amino acid (1.8 equiv); (c) amino acid (6.0 equiv); (d) sulfuric acid was used in place of TFA.

Acknowledgment. I thank Robert Reamer for help with NMR structure assignments and Thomas Novak for HRMS.

Supporting Information Available: Characterization data for compounds **6a**−**f**,**h**, **8a**,**b**, **9c**,**d**, **10**, **11**, and **14**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org

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(12) We thank a reviewer for suggesting this explanation.

(13) The low yields using amino acids other than glycine are unlikely solely due to increased sterics. The Minisci reaction accommodates sterically hindered alkyl radicals as demonstrated by the addition of the *tert*-butyl radical (derived from pivalic acid) in 90% yield under these reaction conditions, see also Samaritoni, J. G. *Org. Prep. Proced. Int.* **1988**, *20*, 117.