

Copper-Catalyzed Perkin—Acyl-Mannich Reaction of Acetic Anhydride with Pyridine: Expeditious Entry to Unconventional Piperidines

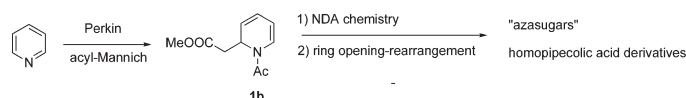
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ABSTRACT



A regioselective introduction of a methoxycarbonyl methyl group at the C₂ position of unsubstituted pyridine has been accomplished with catalytic amounts of copper(II) triflate in mild reaction conditions. The *N*-acetyl-1,2-dihydropyridyl acetic acid methyl ester obtained is a valuable building block for the synthesis of new polyfunctionalized piperidine derivatives bearing unconventional substitution patterns.

The addition of carbon-based nucleophiles to pyridines is a powerful strategy to obtain the piperidine subunit, which is one of the most prominent pharmacophores found in biologically active compounds.¹ It is known that some hard organometallic reagents can react with pyridine at the C-2 position selectively.² Selective functionalizations at the C-2 position have been effected in a catalytic manner through C(2)-H activation of pyridines by transition metal complexes.³ In regard to the addition of metal enolates or

enolate equivalents to pyridines, they have been introduced at the C-2 position only starting from appropriately *substituted* pyridinium derivatives.⁴ When the additions have been performed on *unsubstituted* pyridinium species, a poor regioselectivity, with the predominant formation of 1,4-dihydropyridines, was invariably observed.⁵ Apart from the venerable Perkin reaction,⁶ the use of aliphatic carboxylic acid anhydrides such as carbon nucleophile in aldol or a Mannich-type addition reaction has received only scant attention.⁷ On the other hand, acetic anhydride, most often in combination with pyridine, is a widely used acylation reagent. The isolation of *N*-acetyl-1,2-

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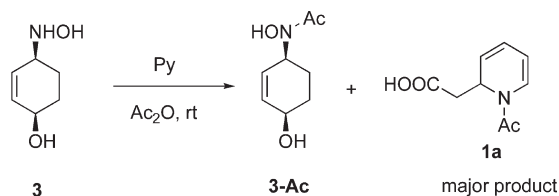
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dihydropyridyl acetic acid (**1**) in very low yields has been reported as an artifact during acetylation reactions using acetic anhydride and pyridine.^{7a,b} We now report the activation of acetic anhydride by means of metal salts to give a simple and practical access to *N*-acetyl-1,2-dihydropyridyl acetic acid. Furthermore, we report simple elaborations of this nucleus to give piperidines with unconventional substitution patterns.

We recently noticed that attempted acetylation of cyclohexenyl hydroxylamino alcohol **3**⁸ in pyridine afforded *N*-acetyl-1,2-dihydropyridine acetic acid **1a** as the major reaction product (Scheme 1). Close examination of the reaction showed that the presence of tiny amounts of copper salts present as impurities in starting compound **3** was responsible for the addition of acetic anhydride to pyridine.

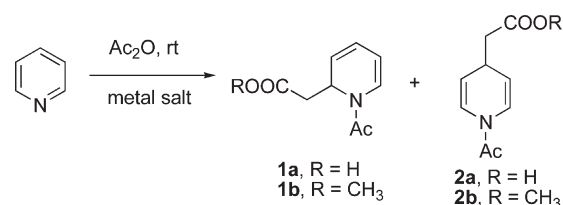
Scheme 1. Unexpected Product from Acetylation Reaction of Compound **3**



Hence, a weighed amount of anhydrous Cu(OTf)₂ was poured into a 1:1 mixture of pyridine and Ac₂O and left to stir overnight. A simple filtration on Celite afforded a crude mixture containing 1,2-dihydropyridine **1a** (85%) and 1,4-dihydropyridine **2** (15%) (entry 1, Table 1). It should be noted that despite the presence of soft enolization methods for ketones and other carboxylic acid derivatives based on the use of Lewis acid–Lewis base systems, nothing similar has been described for a carboxylic acid anhydride.⁹ Lewis acids as promoters for this reaction were also briefly surveyed, evaluating the moles of crude products per mole of catalyst (TON), and the regioisomeric ratios of addition products **1a** and **2a**.

As shown in Table 1, other Lewis acids gave the corresponding addition products, albeit with a lower TON and regioisomeric ratio (entries 4–6). In particular, a good result was obtained with Zn(OTf)₂ (entry 7), while no reaction was observed with highly coordinated copper salts such as CuCl and CuCl₂ (entries 2 and 3). When the mixture was allowed to react for seven days in the presence of Cu(OTf)₂, a significant increase in the TON was obtained (entry 8). The lack of reactivity observed in control experiments in which the metal salt was omitted points to a “soft enolization” pathway, in which the Cu²⁺ salt

Table 1. Screening of Metal Salts As Promoter of the Perkin–Acyl-Mannich Addition^a



entry	Lewis acid	TON ^b	regioisomeric ratio (1a/2a) ^c
1	Cu(OTf) ₂	7	85/15
2	CuCl ₂	–	n.d.
3	CuCl	–	n.d.
4	FeCl ₃	5	70/30
5	Sc(OTf) ₃	2	75/25
6	MgBr ₂	5	68/32
7	Zn(OTf) ₂	6	80/20
8 ^d	Cu(OTf) ₂	15	85/15

^a Reaction carried out at rt using 1.0 mmol of metal salt, pyridine (8.1 mL), and Ac₂O (9.45 mL). After 24 h the reaction was filtered on a pad of Celite and evaporated to dryness. ^b Moles of crude products by weight per mole of catalyst. ^c Determined by ¹H NMR of the crude mixture. ^d Reaction time was 7 d.

coordinates to the carbonyl oxygen of the acetic anhydride to give a copper enolate species **A** after deprotonation of the α-proton by the acetate anion (Scheme 2). The subsequent addition of the in situ generated copper enolate to *N*-acetyl pyridinium ion occurs mainly at the C-2 position, and only this pathway is shown. Addition–elimination of the acetate anion to the in situ formed mixed anhydride **B** established an equilibrium in which compound **1a**, its carboxylate anion, and compound **B** are present. Initial attempts to work up the reaction by partitioning the crude mixture with water and AcOEt proved to be difficult and led to the loss of a large quantity of the products obtained. On the other hand, a simple filtration on Celite did not lead to a satisfactory crude reaction product, as it did not completely remove the metal salt.

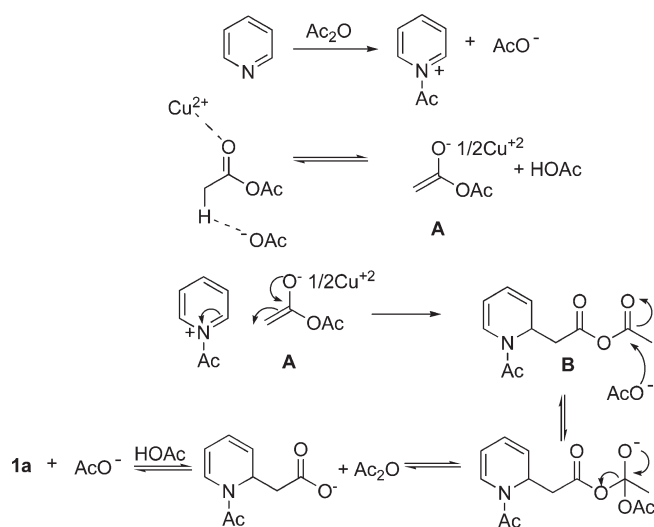
Moreover, compounds **1a** and **2a** were not completely stable during chromatographic purification on silica gel, making separation of the two regioisomers in a pure state difficult. Satisfactory removal of the copper salt was obtained with an aqueous workup in the presence of a saturated aqueous solution of Na₂EDTA. Subsequent

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(9) For recent examples, see: (a) Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 3376–3379. (b) Lim, D.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139–4142. For a seminal paper, see: (c) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877–4879.

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Scheme 2. Plausible Reaction Mechanism for the Copper-Catalyzed Soft Enolization Perkin–Acyl–Mannich Reaction

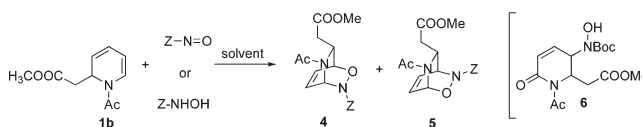


treatment with ethereal diazomethane in a 1:1 mixture of MeOH/Et₂O gave the corresponding methyl esters **1b** and **2b** which were amenable to chromatographic purification on silica gel.

N-Substituted 1,2-dihydropyridines are very useful for the synthesis of a variety of interesting compounds by the use of Diels–Alder type reactions.¹⁰ The nitroso Diels–Alder (NDA) reaction, which has emerged as a powerful tool for stereoselective organic synthesis,¹¹ has rarely been applied to 1,2-dihydropyridines as dienophiles.¹² Hence, the influence of the methoxycarbonyl methyl group at the C₂ position of 1,2-dihydropyridine **1b** using nitroso dienophiles of different kinds on the regioselectivity was examined. As expected, the reaction occurred at the C₃–C₆ position of the diene system in a *trans* fashion with respect to the substituent at the C₂ position, to give cycloadducts of type **4** or **5** depending on the electronic effects of nitroso dienophiles.¹³

In particular, the use of nitrosobenzene gave, with complete regio- and diastereoselectivity, the 3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene **5a** (Table 2, entry 1).^{12,13} In accordance with previous observations, this direct adduct showed some decomposition during chromatographic purification on silica gel.^{12b} The selective obtention of the inverse adduct 2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene **4b** was realized by the use of a phenylacetyl nitroso species

Table 2. Regioselectivity of the Nitroso Diels–Alder Reaction of 1,2-Dihydropyridine **1b**



entry	Z	conditions	ratio (4/5) ^a	yield (%) ^b
1	Ph	CH ₂ Cl ₂ , rt, 1 h	1/99	5a (70) ^c
2	PhCH ₂ CO	NaIO ₄ , MeOH/H ₂ O, 0 °C, 3 h	99/1	4b (65)
3	PhCH ₂ CO	Et ₄ NIO ₄ /CH ₂ Cl ₂ , –78 °C, 3 h	99/1	4b (42)
4	Boc	NaIO ₄ , MeOH/H ₂ O, 0 °C, 3 h	55/45	4c (45) 5c (23)
5	Boc	Et ₄ NIO ₄ /CH ₂ Cl ₂ , –78 °C, 3 h	56/44	4c (32) 5c (15)
6	Boc	CuCl ₂ , H ₂ O ₂ / THF, rt, 2 h	na	4c (46) 6 (30)

^a Determined by ¹H NMR of the crude mixture. ^b Isolated yield after chromatographic purification. ^c A partial retro Diels–Alder (ca. 15%) reaction was found during chromatographic purification.

generated in situ by oxidation of the corresponding hydroxamic acid in both protic and aprotic solvents (entries 2–3).¹⁴ The use of a carbamate-protecting group gave a mixture of adducts **4c** and **5c** which were separable by chromatographic purification on silica gel (entries 4–5). The use of H₂O₂ in combination with catalytic amounts (5 mol %) of CuCl₂ or FeCl₃¹⁵ gave adduct **4c** with an increased isolated yield, but also imide **6** deriving from a ring-opening overoxidation of compound **5c** was obtained (entry 6).

The regioselective introduction of a methoxycarbonyl methyl group at the C₂ position of pyridine opened a new access to cyclic β-amino acids, such as homopipercolic acid derivatives, which have a number of interesting features and have been used to prepare important biologically active compounds.¹⁶ We envisioned that the intrinsic control of the relative stereochemistry of C–N and C–O bond formation during the Diels–Alder reaction of 1,2-dihydropyridine **1b** with nitroso dienophiles could afford polyfunctionalized piperidines after simple manipulation. While the reductive cleavage of the N–O bond of direct phenylnitroso cycloadduct **5a** was plagued by a competitive retro Diels–Alder reaction, the cleavage of the N–O bond of inverse nitroso cycloadducts **4b** and **4c** showed some interesting features with acyl or carbamate protecting groups.

For example, the treatment of N-Boc protected substrate **4b** with a stoichiometric amount of Mo(CO)₆ afforded polyfunctionalized eneacetamide **7c** with 55%

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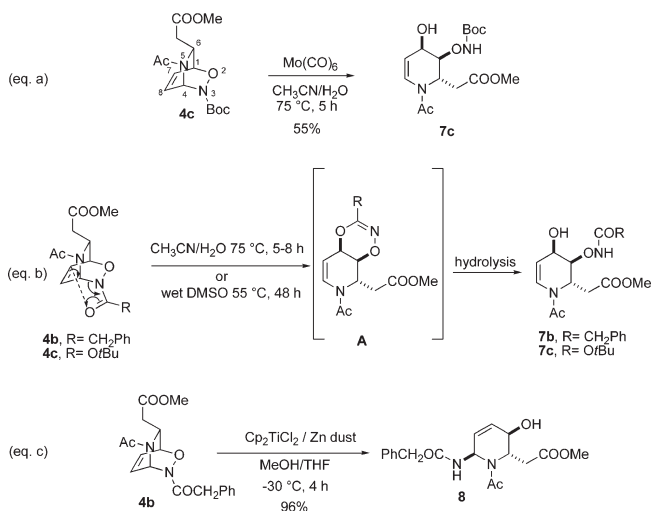
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(14) This opposite regioselectivity has been explained by considering the shape of FMO in arylnitroso and acylnitroso species. See: Streith, J. *Synlett* **1996**, 189–200.

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Scheme 3. Simple Elaborations of Inverse Adducts



isolated yield, instead of the expected product of N–O cleavage (eq a, Scheme 3).¹¹ Subsequent control experiments performed by ¹H NMR in CD₃CN or in CD₃CN/D₂O mixtures with or without molybdenum(0) showed that the presence of water was essential to promote the thermal conversion of cycloadduct **4b** and **4c** into **7c** and **7c**, respectively. The same transformation can be also obtained with wet DMSO at 55 °C for 48 h. The products **7b** and **7c** could arise through a C₄–N₃ bond cleavage via a

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formal [3.3]-sigmatropic rearrangement to give 1,4-dioxazine **A**, followed by hydrolysis (eq b, Scheme 3). A [3.3]-sigmatropic rearrangement has been reported to occur for related amide protected cycloadducts, but not for a carbamate protected cycloadduct, with the isolation of a 1,4-dioxazine.^{13a} The remarkable effect of water on the reaction course could be ascribed to the susceptibility of nonconcerted Claisen-type rearrangements to hydrogen bond acceleration.¹⁷

The use of stoichiometric amounts of Cp₂Ti(III)Cl at low temperatures, recently reported by Miller and co-workers,¹⁸ was decisive to cleave the N–O bond of inverse adduct **4b** without competitive side reactions. The corresponding gem-diamine 1-*N*-iminosugar **8**, an interesting class of iminosugars with glycomimetic properties,¹⁹ was obtained in a quantitative yield (eq c, Scheme 3). On the other hand, N-Boc protected NDA cycloadduct **4c** proved to be scarcely reactive in these reaction conditions.

In conclusion, the carbomethoxy methylation reaction of acetic anhydride with pyridine has been developed to a synthetically useful extent. In this way, unconventional functionalized piperidines can be obtained very easily in a few steps starting from pyridine. Studies are in progress in order to assess the biological activity of simple derivatives of the compounds obtained.

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