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

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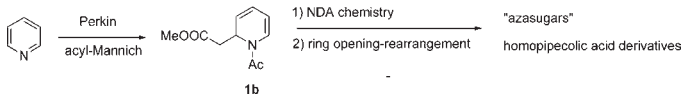
ABSTRACT



A regioselective introduction of a methoxycarbonyl methyl group at the C_2 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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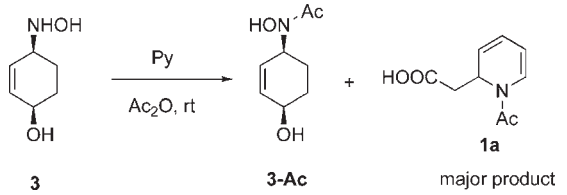
dihydropyridyl acetic acid (**1**) in very low yields has been reported as an artifact during acetylation reactions using acetic anhydride and pyridine.[7a,b] We now report the activation of acetic anhydride by means of metal salts to give a simple and practical access to *N*-acetyl-1,2-dihydropyridyl 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.

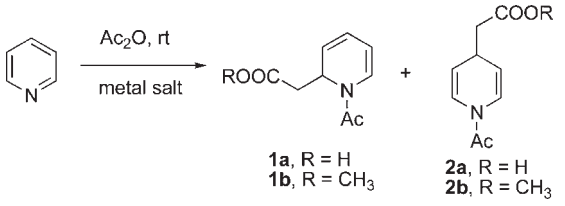
Scheme 1. Unexpected Product from Acetylation Reaction of Compound **3**



Hence, a weighted amount of anhydrous $Cu(OTf)_2$ was poured into a 1:1 mixture of pyridine and Ac_2O 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 $CuCl_2$ (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 Cu^{2+} 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 Ac_2O (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 Na_2EDTA. Subsequent

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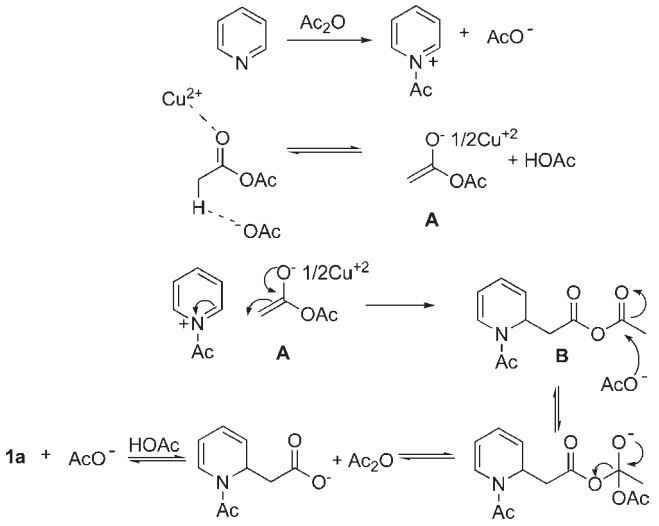
(9) For recent examples, see: (a) Kohler, M. C.; Yost, J. M.; Garnsey, M. R.; Coltart, D. M. *Org. Lett*. **2010**, *12*, 3376–3379. (b) Lim, D.; Zhou, G.; Coltart, D. M. *Org. Lett*. **2007**, *9*, 4139–4142. For a seminal paper, see:(c) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem*. **1985**,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

(10) For leading examples, see: (a) Pipecolic acid: Lemire, A.; Charette, A. B. *J. Org. Chem*. **2010**, *75*, 2077–2080. (b) (−)-Oseltamivir: Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron* **2010**, *65*, 3229–3245. (c) *Iboga* alkaloids: Weinstein, B.; Chang Lin, L.-C.; Fowler, F. W. *J. Org. Chem*. **1980**, *45*, 1657–1661. (d) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem*. **1990**, *55*, 6028–6037. (e) Reserpine: Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc*. **1980**, *102*, 6157–6159. (f) Homoepibatidines: Krow, G. R.; Cheung, O. H.; Hu, Z.; Huang, Q.; Hutchinson, J.; Liu, N.; Nguyen, K. T.; Ulrich, S.; Yuan, J.; Xiao, Y.; Wypij, D. M.; Zuo, F.; Carroll, P. J. *Tetrahedron* **1999**, *55*, 7747–7756. *Lycopodium* alkaloids: Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett*. **1999**, *1*, 229–231.

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

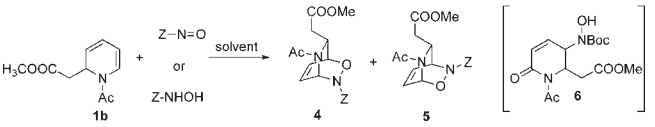


treatment with ethereal diazomethane in a 1:1 mixture of MeOH/Et_2O gave the corresponding methyl esters **1b** and **2b** which were amenable to chromatographic purification on silica gel.

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 C_2 position of 1,2-dihydropyridine **1b** using nitroso dienophiles of different kinds on the regioselectivity was examined. As expected, the reaction occurred at the C_3–C_6 position of the diene system in a *trans* fashion with respect to the substituent at the C_2 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 obtainment 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_2Cl_2, rt, 1 h	1/99	**5a** (70)[c]
2	$PhCH_2CO$	$NaIO_4$, MeOH/H_2O, 0 °C, 3 h	99/1	**4b** (65)
3	$PhCH_2CO$	Et_4NIO_4/CH_2Cl_2, −78 °C, 3 h	99/1	**4b** (42)
4	Boc	$NaIO_4$, MeOH/H_2O, 0 °C, 3 h	55/45	**4c** (45) **5c** (23)
5	Boc	Et_4NIO_4/CH_2Cl_2, −78 °C, 3 h	56/44	**4c** (32) **5c** (15)
6	Boc	$CuCl_2$, H_2O_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 H_2O_2 in combination with catalytic amounts (5 mol %) of $CuCl_2$ or $FeCl_3$[15] 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 C_2 position of pyridine opened a new access to cyclic β-amino acids, such as homopipecolic 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%

(11) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630–5647.

(12) (a) Knaus, E. E.; Avasthi, K.; Giam, C. S. *Can. J. Chem.* **1980**, *58*, 2447–2451. (b) Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 2368–2371. For a catalytic asymmetric version, see: (c) Jana, K. C.; Grimme, S.; Studer, A. *Chem.—Eur. J.* **2009**, *15*, 9078–9084.

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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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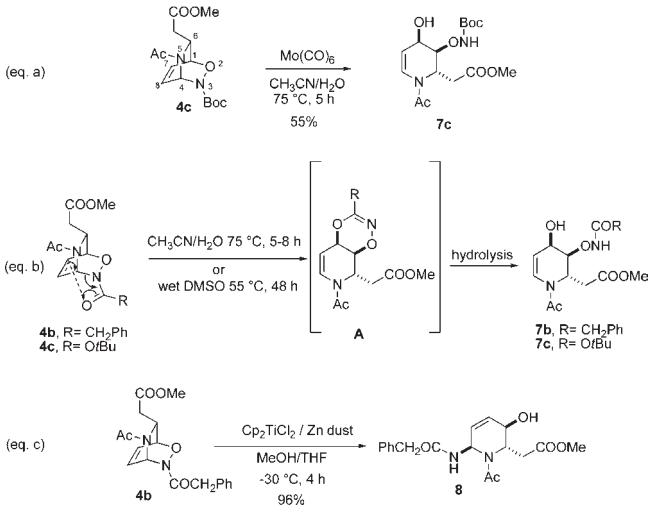
(16) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809–823.

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 ^{1}H NMR in CD_3CN or in CD_3CN/D_2O 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 C_4-N_3 bond cleavage via a 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 $Cp_2Ti(III)Cl$ at low temperatures, recently reported by Miller and coworkers,[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.

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