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A Modified Mannich-Type Reaction Catalyzed by VO(acac)$_2$

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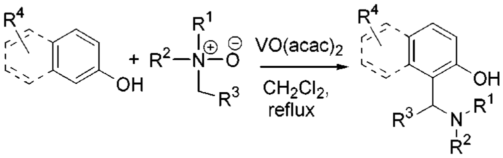
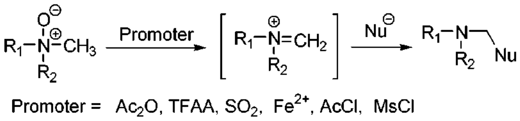
ABSTRACT



A facile VO(acac)$_2$-catalyzed in situ generation of iminium ions from amine *N*-oxides and their participation in a modified Mannich-type reaction is described.

The Mannich reaction[1] is an important carbon−carbon bond formation reaction widely used in the synthesis of secondary and tertiary amine derivatives and applied as a key step in the synthesis of many bioactive molecules and complex natural products.[2] This reaction basically involves the addition of a carbon nucleophile to an iminium ion, resulting in a secondary or tertiary amine derivative depending on the nature of the substrate. Among the several methods available for the generation of the required iminium ions, the commonly used procedure is the Polonovsky or modified Polonovsky reaction[3] in which a tertiary amine oxide is treated with a promoter such as acetic anhydride, trifluoroacetic anhydride,[4] sulfur dioxide,[5] or ferrous salt[6] (Scheme 1). However, these promoters are expensive or are sometimes difficult to handle and are required in more than stoichiometric amounts. Recently acetyl chloride and mesyl chloride[7] were used as activating agents in excess amounts in a Polonovsky−Potier reaction of Berbine *N*-oxides; however, the procedure suffered from very poor yields.

Scheme 1



Though vanadium-catalyzed oxidation of amine to amine oxide was previously reported,[8] vanadium-mediated generation of the iminium ion from amine *N*-oxide was hitherto unreported. Earlier, we investigated the vanadium-catalyzed homo-coupling of phenols and naphthols in the presence of an external co-oxidant.[9] During the course of our studies toward finding an ideal combination of vanadium oxidant

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(1) (a) Tramontini, M.; Angiolini, L. *Mannich Bases: Chemistry and Uses*; CRC: Boca Raton, FL, 1994. (b) Tramontini, M. *Synthesis* **1973**, 703. (c) Blicke, F. F. *Org. React. (NY)* **1942**, *1*, 303. (d) Overman, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 1007. (e) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045. (f) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (g) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.

(2) (a) Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241. (b) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (c) Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3*, 703.

(3) (a) Polonovsky, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190. (b) Leonard, N. J.; Klainer, J. A. *J. Heterocycl. Chem.* **1971**, *8*, 215. (c) Leonard, N. J.; Paukstelis. J. V. *J. Org. Chem.* **1963**, *28*, 3021.

(4) Ahond, A.; Cavé, A.; Kan-Fan, C.; Husson, H.-P.; de Rostolan, J.; Potier, P. *J. Am. Chem. Soc.* **1968**, *90*, 5622.

(5) Edward, J. T.; Whiting, J. *Can. J. Chem.* **1971**, *49*, 3502.

(6) Ferris, J. P.; Gerwe, R. D.; Gapski, G. R. *J. Am. Chem. Soc.* **1967**, *89*, 5270.

(7) Suau, R.; Najera, F.; Rico, R. *Tetrahedron* **2000**, *56*, 9713.

(8) (a) Kuhnen, L. *Chem. Ber.* **1966**, *99*, 3384. (b) Sheng, M. N.; Zajacek, J. G. *J. Org. Chem.* **1966**, *33*, 588.

(9) (a) Hwang, D.-R.; Chen, C.-P.; Uang, B.-J. *Chem. Commun.* **1999**, 1207. (b) Chu, C.-Y.; Hwang, D.-R.; Wang, S.-K.; Uang, B.-J. *Chem. Commun.* **2001**, 980.

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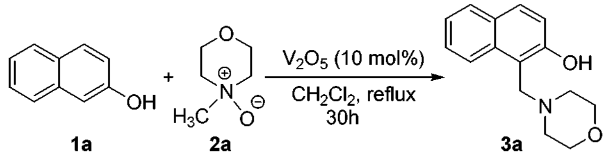
and external co-oxidant for the oxidative coupling reactions, we performed an equimolar reaction of 2-naphthol (**1a**) and *N*-methylmorpholine *N*-oxide (NMO) (**2a**) in the presence of 10 mol % of V_2O_5 in dichloromethane under refluxing conditions (Scheme 2). To our pleasant surprise, the corresponding Mannich adduct **3a** was obtained in good yield in this reaction. We have developed this vanadium-catalyzed reaction into an expedient general method for the in situ generation of iminium ions from tertiary amine *N*-oxides for their subsequent application in a modified Mannich-type reaction and the results are described in this Letter.

Scheme 2



Catalytic profiles of vanadium(IV) and vanadium(V) species such as $VO(O^iPr)_3$, $VO(acac)_2$, and $VOSO_4 \cdot H_2O$ were tested to optimize the reaction conditions (Table 1). An excellent yield of the Mannich base could be attained in a shorter reaction time when $VO(acac)_2$ was used as catalyst. The yield of the product could be further upgraded by increasing the amount of NMO to 3 equiv.

Table 1. Preparation of the Mannich Base from 2-Naphthol (**1a**) and NMO (**2a**) Using Vanadium Catalysts[a]

entry	catalyst	time (h)	yield (%)
1	V_2O_5	30	78
2	$VO(O^iPr)_3$	16	78
3	$VO(acac)_2$	8	92
4	$VOSO_4 \cdot 2H_2O$	24	52

[a] Reaction conditions: catalyst (10 mol %), CH_2Cl_2, reflux.

In a preliminary assessment of the generality of this reaction, we tested several naphthols and phenols as nucleophiles in this Mannich-type reaction (Scheme 3). Similar yields and reactivities were observed with bromo- and methoxy-substituted 2-naphthols (Table 2, entries 3 and 4), while ester-substituted 2-naphthol (entry 5) afforded the corresponding Mannich base in a relatively low yield. 1-Naphthol and phenols also furnished the corresponding Mannich bases albeit in low yields. Under similar reaction conditions, trimethylamine *N*-oxide (TMNO) (**2b**) smoothly reacted with 2-naphthol and phenol in the presence of $VO(acac)_2$ to provide the corresponding Mannich adducts **3**. This iminium species generated from TMNO is an equivalent of Eschenmoser salt.[10]

Scheme 3

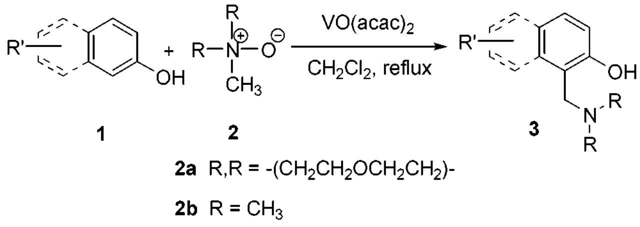
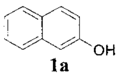
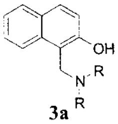
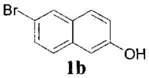
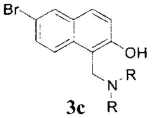
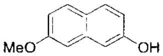
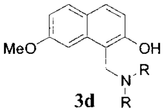
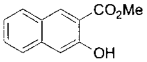
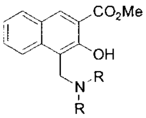
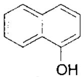
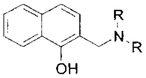
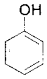
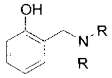
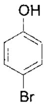
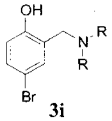
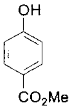
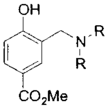


Table 2. Reactions of Naphthols and Phenols with Amine *N*-Oxide Catalyzed by $VO(acac)_2$

entry	ArOH	amine *N*-oxide	time (h)	product[a]	yield (%)
1	 **1a**	NMO	8	 **3a**	92
2		TMNO	24	**3b**	78
3	 **1b**	NMO	8	 **3c**	84
4	 **1c**	NMO	8	 **3d**	81
5	 **1d**	NMO	72	 **3e**	61
6	 **1e**	NMO	8	 **3f**	58
7	 **1f**	NMO	48	 **3g**	37
8		TMNO	24	**3h**	82
9	 **1g**	NMO	48	 **3i**	33
10	 **1h**	NMO	120	 **3j**	43

[a] For entries 2 and 8: R = CH_3. For the remaining entries: R, R = $-(CH_2CH_2OCH_2CH_2)-$; NMO = *N*-methylmorpholine *N*-oxide, TMNO = trimethylamine *N*-oxide.

Taking the reaction of 2-naphthol (**1a**) and *N*-oxide (**2a**) as an illustrative case, a plausible mechanism for this reaction is depicted in Scheme 4. Complexation of the vanadium

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(10) (a) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330. (b) Bryson, T. A.; Bonitz, G. H.; Reichel, C. J.; Dardis, R. E. *J. Org. Chem.* **1980**, *45*, 524. (c) Kinast, G.; Tietze, L.-F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239. (d) Rochin, C.; Babot, O.; Dunoguès, J.; Duboudin, F. *Synthesis* **1986**, 228. (e) Reissig, H.-U.; Lorey, H. *J. Chem. Soc., Chem. Commun.* **1986**, 269.

Scheme 4

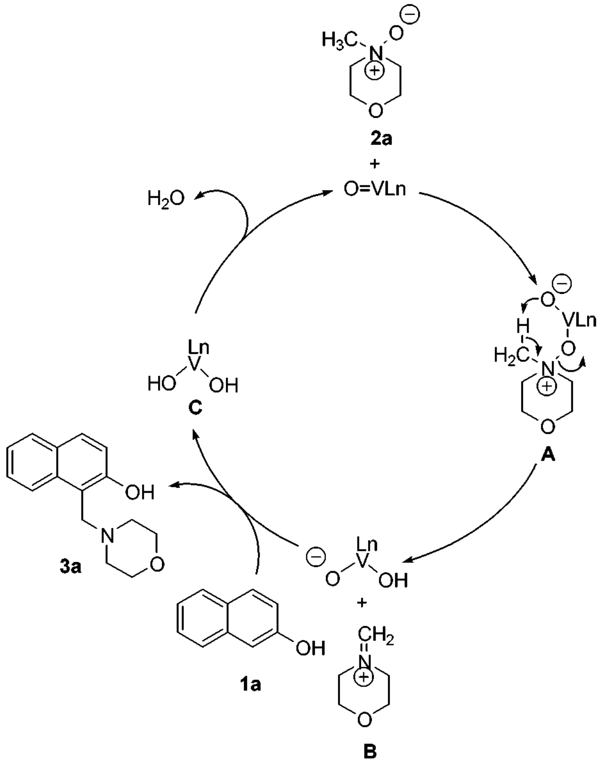
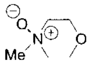
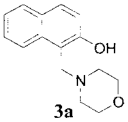
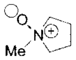
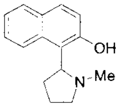
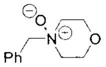
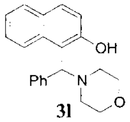
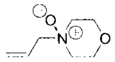
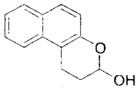
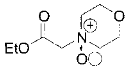
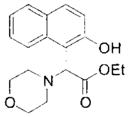
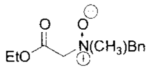
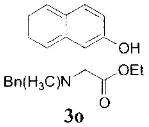


Table 3. VO(acac)$_2$-Catalyzed Modified Mannich-Type Reactions of 3° Amine Oxides with Naphthols

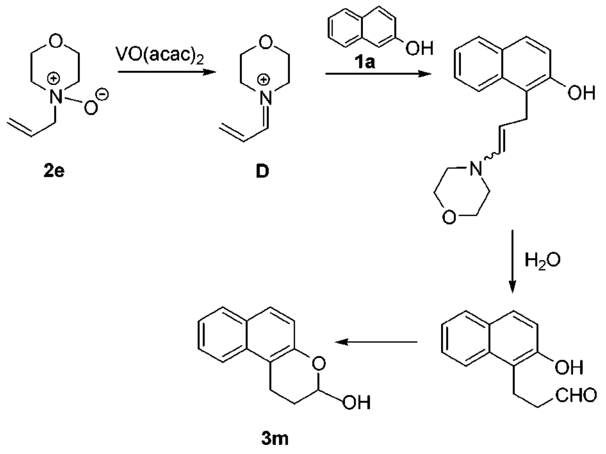
$$\underset{3\text{ eq}}{3^\circ\text{ amine oxide}} + \underset{1\text{ eq}}{2\text{-naphthol}} + \underset{10\text{ mol\%}}{\text{VO(acac)}_2} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{product}$$

entry	3° amine *N*-oxide	temp. (°C)	time (h)	product	yield (%)
1	 **2a**	reflux	8	 **3a**	92
2	 **2c**	reflux	48	 **3k**	64
3	 **2d**	reflux	48	 **3l**	63
4	 **2e**	reflux	48	 **3m**	52
5	 **2f**	25	4	 **3n**	81
6	 **2g**	25	12	 **3o**	70

species with amine *N*-oxide **2a** followed by an intramolecular elimination through six-membered transition structure **A** resulted in iminium ion **B**. Subsequent addition of the naphtholate (obtained from the acidic proton abstraction of 2-naphthol (**1a**) by vanadium species) to the iminium ion **B** results in Mannich base **3a**. The protonated vanadium species **C** then eliminates one molecule of water to regenerate the oxovanadium catalyst.

Site selectivity in this reaction was studied by conducting the reaction of various amine *N*-oxides with 2-naphthol in the presence of a catalytic amount of VO(acac)$_2$ (Table 3). When pyrrolidine *N*-oxide (**2c**) was employed, C−C bond formation took place from the *endo* position. On the other hand, *N*-substituted-morpholine *N*-oxides (**2a**, **2d**, and **2f**) afforded *exo*-addition products. Interestingly, *N*-allylmorpholine *N*-oxide (**2e**) gave hemiacetal **3m**, whose formation can formally be explained by a three-step sequence, 1,4-addition of 2-naphthol (**1a**) to the α,*β*-unsaturated iminium ion intermediate **D** followed by hydrolysis and subsequent hemiacetal formation (Scheme 5). *N*,*N*-Disubstituted glycinate *N*-oxides were found to be more reactive as they could furnish the Mannich base even at room temperature (entries 5 and 6). It is noteworthy that these glycinate *N*-oxides exibited high regioselectivity with the selective participation of active methylene carbon (α to the ester carbonyl) in the formation of Mannich base. Another significant feature of this protocol is that it involves an umpolung-type reaction facilitating the incorporation of an aryl substituent at the α-position of the α-amino acid. Ours is the first metal-catalyzed modified Polonovsky reaction and provides a new entry to α-aryl-α-amino acids. Recently the Risch group reported in situ generation of ternary iminium salts from benzotriazole-based ethyl glyoxylate aminals by using a stoichiometric amount of Lewis acid (AlCl$_3$ or TiCl$_4$) in the synthesis of α-aryl-α-amino acid esters.[11] The classical

Scheme 5



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[11] Grumbach, H.-J.; Merla, B.; Risch, N. *Synthesis* **1999**, 1027.

Mannich reaction had limited applicability in the synthesis of these amino acids.[11]

An interesting double alkylation reaction of the imine carbon was witnessed when 1,3-dicarbonyl compounds such as dibenzoylmethane (**4a**) and diethyl malonate (**4b**) were reacted with NMO or TMNO (Scheme 6, Table 4). Initial Mannich reaction followed by a β-elimination of an amine from the Mannich base to form an α,β-unsaturated compound and subsequent Michael addition of a second molecule of 1,3-dicarbonyl compound would rationalize the formation of a double alkylation product in these reactions.

Scheme 6

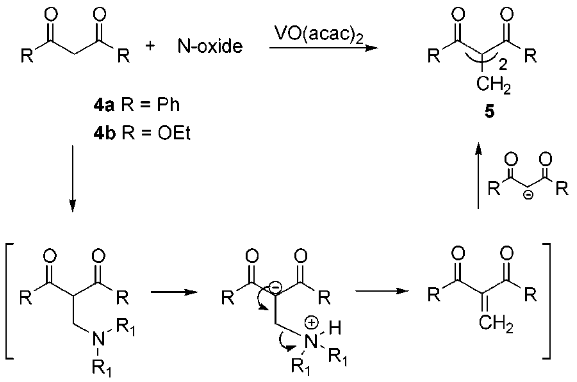

Table 4. Reaction of 1,3-Dicarbonyl Compounds with Amine *N*-Oxides

entry	substrate	*N*-oxide	time (h)	product	yield (%)
1	**4a**	NMO	14	**5a**	56
2		TMNO	10		77
3	**4b**	TMNO	24	**5b**	54

In conclusion, we have devised a general and convenient $VO(acac)_2$-catalyzed method for the facile in situ generation of iminium ions from various amine oxides, for their usage in Mannich-type reactions. The formation of a C═N bond is highly regioselective, selectively involving the carbon-bearing more acidic proton. Viability of this approach for the conversion of different types of amine *N*-oxides into iminium ions promises a wide scope to access a variety of Mannich bases.

Acknowledgment. We are grateful to the National Science Council, Republic of China for financial support of this work.

Supporting Information Available: Detailed experimental procedure and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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