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Synthesis of Furopyridines via Cycloaddition of Unactivated Nitriles with Tungsten-Substituted 1,3-Diene

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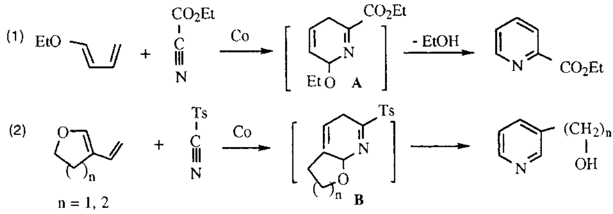
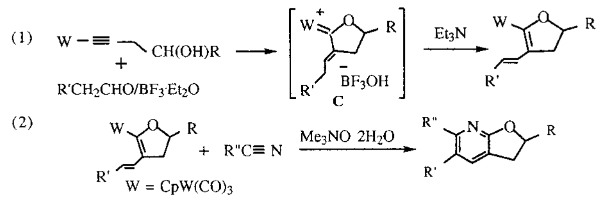
Dials−Alder cycloaddition is recognized as one of the most valuable reactions in organic synthesis;[1−6] it is widely applicable to a variety of dienophiles such as olefins, alkynes, aldehydes, ketones, imines, *N*-acylimines, and nitroso compounds.[1−6] Most of these dienophiles do not require an activating group to achieve cycloadditions under ambient conditions. Cycloadditions of organic dienes with unactivated nitriles proceed only with extreme difficulty except with prolonged heating at high temperatures (>350 °C) to afford pyridine exclusively.[3] Under such conditions, intermolecular Diels−Alder cycloaddition of organic dienes becomes a serious problem. Only highly electron-deficient nitriles such as TsCN and $NCCO_2R$ appear to be good dienophiles at ambient conditions.[7] Cobalt catalyst CpCo(COD)[8] (COD = cyclooctadiene) effects the cycloaddition of alkoxydiene with TsCN to give a good yield of pyridines at 50 °C (eq 1 of Scheme 1), but the reaction fails to proceed with common aliphatic and aryl nitriles. [4 + 2] Cycloaddition of unactivated nitriles at ambient conditions remains a challenging issue in synthetic organic chemistry.

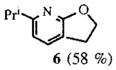
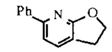
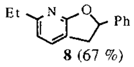
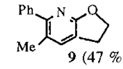
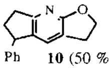
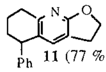
The furopyridine functionality has emerged as a useful pharmacophore in several therapeutic areas including treatment of skin disease and relief of intraoccular pressure among others.[9,10] A straightforward synthesis of this functionality via cyano [4 + 2] cycloaddition is prohibited by kinetic instability of intermediate **B** that forms pyridine with cleavage of the C−O bond (eqs 1 and 2 of Scheme 1).[8b] In this paper, we report a remarkably feasible cyano [4 + 2] cycloaddition at 23 °C and its application to synthesis of furopyridines. Most importantly this reaction is applicable to unactivated nitriles in both inter- and intramolecular fashions.

Scheme 1



Scheme 2



Entry	Dienes	R"CN	Cond.	Products
1	R = R' = H **1**	R" = Pr^i	$Me_3NO\ 2H_2O$ 23 °C (8 h)	 **6** (58 %)
2	R = R' = H **1**	R" = Pr^i	hv (23 °C, 48 h)	**6** (47%)
3	R = R' = H **1**	R" = Ph	$Me_3NO\ 2H_2O$ 23 °C (8 h)	 **7** (82 %)
4	R = Ph, R' = H **2**	R" = Et	$Me_3NO\ 2H_2O$ 23 °C (8 h)	 **8** (67 %)
5	R = H, R' = Me **3**	R" = Ph	$Me_3NO\ 2H_2O$ 23 °C (8 h)	 **9** (47 %)
6	R = H R' = $\underset{\text{Ph}}{\text{CH}}\text{-}(CH_2)_2CN$ **4**	—	$Me_3NO\ 2H_2O$ CH_2Cl_2 (reflux, 42 h)	 **10** (50 %)
7	R = H R' = $\underset{\text{Ph}}{\text{CH}}\text{-}(CH_2)_3CN$ **5**	—	$Me_3NO\ 2H_2O$ CH_2Cl_2 (reflux, 12 h)	 **11** (77 %)

Shown in Scheme 2 (eq 1) is the general synthetic protocol for the starting tungsten-η^1-dienes **1**−**5** involving the cycloalkenation[11] of tungsten−alkynols with $R'CH_2CHO$, followed by deprotonation of the resulting tungsten−oxacarbenium **C** with excess Et_3N; the yields of **1**−**5** exceeded 87%. Further use of these dienes to achieve a cyano [4 + 2] cycloaddition at 23 °C are illustrated in Scheme 2. A variety of unactivated nitriles are applicable to the reactions including aliphatic nitriles RCN (R = Et, Pr^i) and benzonitrile that are used as reaction solvents (entries 1−5). In entries 1 and 2, the reaction is activated by either $Me_3NO{\cdot}2H_2O$ (5.0 equiv) or by photolysis (λ = 300 nm); the former was more effective to yield furopyridines **6** in a better yield (58%).

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(5) For representative examples of transition-metal-catalyzed Diels−Alder reaction in non-Lewis acid pathway, see: (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (b) Mckinstry, L.; Livinghouse, T. *Tetrahedron Lett.* **1994**, *50*, 6145. (c) tom Dieck, H.; Diercks, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 778. (d) Garratt, P. J.; Wyatt, M. *J. Chem. Soc., Chem. Commun.* **1974**, 251. (e) Gibertson, S. R.; Zhao, X.; Dawson, D. P.; Marshall, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 8517.

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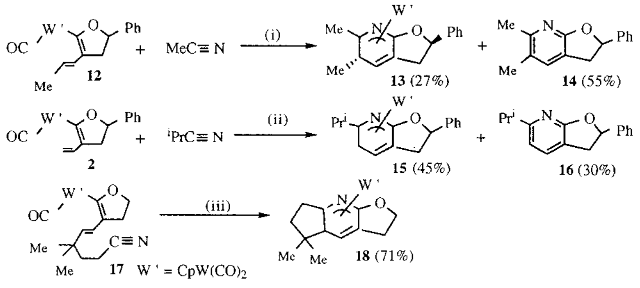
Scheme 3[a]



[a] (i) 23 °C, 70 h; (ii) $Me_3NO\cdot 2H_2O$ (5.0 equiv), 23 °C (12 h); (iii) $Me_3NO\cdot 2H_2O$ (5.0 equiv), CH_2Cl_2, reflux, 20 h.

The cycloaddition also effects the synthesis of disubstituted pyridine **9** in 47% yield (entry 5). We also prepared tungsten-η^1-dienes **4** and **5** bearing a tethered nitrile to realize an intramolecular [4 + 2] cycloaddition reaction. Heating **4** and **5** with $Me_3NO\cdot 2H_2O$ (5.0 equiv) in refluxing CH_2Cl_2 for 12 h afforded tricyclic furopyridines **10** and **11** in 50% and 77% yields, respectively.

One question remaining here is the loss of tungsten fragment during furopyridine syntheses. Thus, we sought to isolate the key organometallic intermediates to ensure a cyano [4 + 2] cycloaddition pathway. The attempts are successful with selection of suitably sized R′ and R″ on the reactants as depicted in Scheme 3. Photolysis of compound **12** (λ = 300 nm) in CH_3CN at 23 °C afforded tungsten−π-2-azaallyl complex **13** as a single diastereomer in 27% yield in addition to furopyridine **14** (55%). The lack of other stereoisomers of **13** is probably due to their kinetic instabilities, easily forming furopyridines. Similarly, treatment of compound **2** with $Me_3NO\cdot H_2O$ (5.0 equiv) in isobutyronitrile (23 °C, 12 h) produced tungsten−π-azaallyl **15** as a mixture of cis and trans isomers (trans/cis = 3/1) in 45% yield; the furopyridine **16** was obtained in 30% yield. Separation of the cis/trans isomers of **15** was conducted on a cold florisil column (−20 °C). Heating the π-allyl complexes **13** and **15** with $Me_3NO\cdot 2H_2O$ (5.0 equiv) in refluxing CH_2Cl_2 for 72 h afforded the furopyridines **14** and **16** in 85% and 87% yields, respectively. A tricyclic tungsten−azaallyl species **18** was also obtained as a single diastereomer in 71% yield through an intramolecular cyano [4 + 2] cycloaddition of tungsten-η^1-diene **17** (eq 3 of Scheme 3). The molecular structures of compound **13** and the cis and trans isomers of **15** were determined by an X-ray diffraction study.[12,13] The ORTEP drawing of **13** (Figure 1) reveals that $CpW(CO)_2$ fragment is bound to the furopyridine moiety in a π-2-azaallyl fashion with the W−C(3) [2.321(6) Å], W−N [2.140(5) Å], and W−C(7) [2.307(6) Å] distances; the C(5)−C(6) length [1.314(8) Å] represents a C−C double bond. The phenyl and methyl groups of **13** are in the cis and trans orientations, respectively, relative to tungsten fragment.

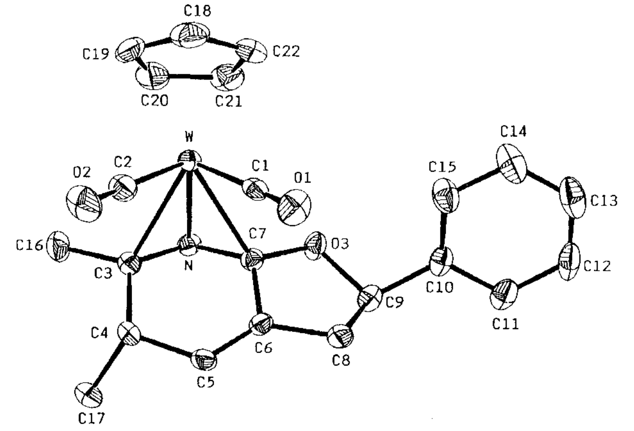
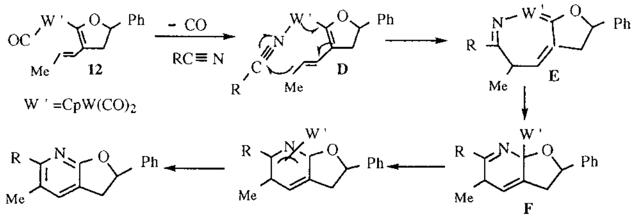


Figure 1. ORTEP drawing of tungsten−π-azaallyl complex **13** and its pertinent distances (Å): W−C(3) = 2.321(6), W−N = 2.140(5), W−C(3) = 2.321(6), C(3)−N = 1.399(8), C(7)−N = 1.374(7), C(5)−C(6) = 1.314(8).

Scheme 4



The highly feasible [4 + 2] cycloadditions of unactivated nitriles are expected to be closely associated with the role of the tungsten metal. A plausible mechanism is proposed for Scheme 4. We envision that tungsten−diene **12** is required to lose a CO group to uptake a RCN group to initiate the reaction; the coordinated nitrile of **D** is reactive toward inter- or intramolecular attack of nucleophiles.[14] Under nitrile coordination, the CpW(CO)$_2$ fragment promotes an intramolecular attack of the diene =CHR carbon at the nitrile carbon through donation of its d-electrons, forming a seven-membered heterocycle like tungsten carbene **E** that is stabilized by the furan oxygen. A subsequent insertion of the single W−N bond of **E** into its W=C carbene carbon generates the 16e Diels−Alder adduct **F**, further yielding π-azaallyl complex via coordination of tungsten to the less hindered C=N bond. Although only one literature paper is reported for insertion of the M−N bond into M=C group,[15] we cannot exclude its role here. A concerted [4 + 2] cycloaddition[1] between a coordinated nitrile and a η^1-diene moiety is unlikely to occur because of their unfavorable orientations for orbital overlap.

In summary, we disclose here a facile [4 + 2] cycloaddition of aliphatic and aryl nitriles in both inter- and intramolecular systems; the examples are highlighted by their application to synthesis of furopyridines. The organometallic principles in this cycloaddition are helpful to design a metal-catalyzed synthesis of pyridines from common aliphatic nitriles. Studies in this direction are in progress.

Acknowledgment. We gratefully acknowledge financial support of this work from the National Science Council, Republic of China.

Supporting Information Available: Synthesis and spectral data of compounds **1**−**16**; tables of crystal data, atomic coordinates, bond distances and angles of **13** and **15** (15 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) Crystal data for **13**: monoclinic space group, $P2_1/c$, $a = 14.000(3)$ Å, $b = 8.1414(14)$ Å, $c = 16.945(3)$ Å, $\beta = 100.492(14)°$, $V = 1899.1(6)$ Å^3, $Z = 4$. Of the 3335 unique reflections, 2853 were considered observed having $I > 2\sigma(I)$. Final $R = 0.030$, $R_w = 0.035$.

(13) Crystal data for the cis isomer of **15**: monoclinic space group, $P2_1/n$, $a = 10.645(3)$ Å, $b = 9.658(4)$ Å, $c = 19.930(6)$ Å, $\beta = 93.257(24)°$, $V = 2045.6(12)$ Å^3, $Z = 4$. Of the 3603 unique reflections, 2491 were considered observed having $I > 2\sigma(I)$. Final $R = 0.025$, $R_w = 0.028$. Crystal data for the trans isomer of **13**: triclinic space group, $P1$, $a = 9.071(5)$ Å, $b = 10.620(3)$ Å, $c = 12.163(6)$ Å, $\alpha = 112.15(3)°$, $\beta = 109.68(3)°$, $\gamma = 94.47(3)°$, $Z = 2$, $V = 993.2(8)$ Å^3. Of the 3487 unique reflections, 3008 were considered observed having $I > 2\sigma(I)$. Final $R = 0.060$, $R_w = 0.076$.

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(15) Ahn, S.; Mary, A. *J. Am. Chem. Soc.* **1996**, *118*, 7408.