Copper-Exchanged Tungstophosphoric Acid: An Efficient and Reusable Heteropoly Acid for the Synthesis of 2,3,4,5-Tetrahydro-4-methylidenefuran Derivatives

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Copper-exchanged tungstophosphoric acid (Cu-TPA) is found to catalyze efficiently the coupling of propargyl alcohol (prop-2-yn-1-ol) with (arylmethylidene)malononitriles to afford the corresponding 2,3,4,5-tetrahydro-4-methylidenefuran derivatives in good yields and with high selectivity. The catalyst is recycled and reused for three-to-four subsequent runs with a minimal decrease of activity.

Introduction. – In recent years, the use of solid-acid catalysts has received considerable interest in different areas of organic synthesis [1]. The heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts, as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation or without activation, thereby rendering the process economically viable [2][3]. In several cases, heterogeneous catalysts can be recovered with only minor changes in activity and selectivity so that they can be conveniently used in continuous-flow reactions. Among heterogeneous catalysts, heteropoly acids (HPAs) are most attractive, due to their unique properties such as well-defined structure, *Brønsted* acidity, possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, *etc*. [4–12]. To the best of our knowledge, there is no report on the use of Cu salt of a heteropoly acid for the synthesis of 2,3,4,5-tetrahydro-4-methylidenefuran derivatives.

Results and Discussion. – Herein, we report a mild, selective, and efficient method for the synthesis of 2,3,4,5-tetrahydro-4-methylidenefuran derivatives. In a model experiment, benzylidenepropanedinitrile (**1a**) was treated with propargyl alcohol (prop-2-yn-1-ol; **2**) in the presence of 10 mol-% of cupper-exchanged tungstophosphoric acid (Cu-TPA) in MeCN (*Scheme*). The reaction was complete within 3 h at room temperature, and the product, 4,5-dihydro-4-methylidene-2-phenylfuran-3,3(2*H*)-dicarbonitrile (**3a**) was isolated in 87% yield (*Table*, *Entry 1*).

No side-products were detected under these conditions. Encouraged by this result, we turned our attention to various (arylmethylidene)malononitriles **1** with propargyl alcohol (prop-2-yn-1-ol; **2**). Interestingly, (4-F-, 4-Br-, 4-NO$_2$-, 4-Me-, 4-MeO-, 3-NO$_2$-, 2-NO$_2$-, phenylmethylidene)malororitriles (**1b** – **1h**, resp.), (6-bromo-1,3-benzodioxol-

Scheme. *Synthesis of 2,3,4,5-Tetrahydro-4-methylidenefuran Derivatives* **3**

R = phenyl, napthyl, furyl
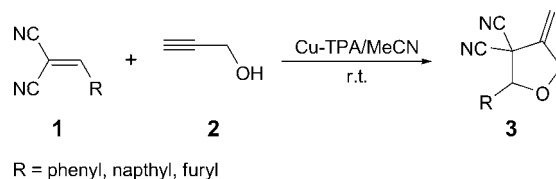
Table. *One-Pot Synthesis of 2,3,4,5-Tetrahydro-4-methylidenefuran Derivatives* **3**
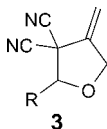
Entry	Product	R	Time [h]	Yield [%]
1	**3a**	Ph	3.0	87
2	**3b**	$4\text{-F–C}_6\text{H}_4$	2.5	90
3	**3c**	$4\text{-Br–C}_6\text{H}_4$	2.3	94
4	**3d**	$4\text{-O}_2\text{N–C}_6\text{H}_4$	1.5	95
5	**3e**	$4\text{-Me–C}_6\text{H}_4$	4.0	85
6	**3f**	$4\text{-MeO–C}_6\text{H}_4$	4.5	83
7	**3g**	$3\text{-O}_2\text{N–C}_6\text{H}_4$	1.5	92
8	**3h**	$2\text{-O}_2\text{N–C}_6\text{H}_4$	1.5	93
9	**3i**	6-Br-1,3-benzodioxol-5-yl	3.0	86
10	**3j**	$2,4\text{-Cl}_2\text{–C}_6\text{H}_3$	2.0	92
11	**3k**	$2,3,4\text{-(MeO)}_3\text{–C}_6\text{H}_2$	3.0	86
12	**3l**	Naphthalen-2-yl	2.5	82
13	**3m**	Furan-2-yl	4.5	78
14	**3n**[a])	Thiophen-2-yl	4.5	74

[a]) COOEt instead of CN at C(3).

5-yl)methylidene)malononitrile (**3i**), reacted smoothly with **2** under similar conditions, and the corresponding products were obtained in good yields (*Table*, *Entries 2 – 12*).

Moreover, (2-(furan-2-ylmethylidene)propanedinitrile (**1m**) afforded the 4,5-dihydro-4-methylidene-2,2′-bifuran-3,3(2*H*)-dicarbonitrile (**3m**; *Table*, *Entry 13*) in good yield. This result provided the incentive for further study of reactions with different *Michael* acceptors. Interestingly, diethyl (thiophen-2-ylmethylidene)propanedioate (**1n**) reacted effectively with **2** under similar conditions to afford diethyl 4,5-dihydro-4-methylidene-2-(thiophen-2-yl)furan-3,3(2*H*)-dicarboxylate (**3n**; *Table*, *Entry 14*). In all cases, the reactions proceeded smoothly at ambient temperature with high selectivity. However, in the absence of catalyst, the reaction did not yield any product even after a long reaction time (15 – 20 h). As solvent, MeCN gave the best results. Enhanced reaction rates, excellent yields, and high selectivity are the features of this method. Products were characterized by NMR, IR, and MS data. The advantage of the use of Cu-TPA is that it can be easily recovered and recycled in subsequent runs.

Since the mixture is heterogeneous, the catalyst could be easily separated by simple filtration. The recovered catalyst was further washed with Et$_2$O, dried at 60° under reduced pressure, and reused in three to four successive runs with only a minimal decrease in activity. For example, 2-benzylidenepropane-1,3-dinitrile (**1a**) and propargyl alcohol (**2**) in the presence of 10 mol-% of Cu-TPA in CH$_2$Cl$_2$ gave the product **3a** in 87, 85, 82, and 80% yields over four cycles.

Conclusions. – In summary, we have developed an efficient method for the synthesis of 4-(arylmethylidene)tetrahydrofuran derivatives **3** with (arylmethylidene)malononitriles **1** and propargyl alcohol (**2**) using Cu-exchanged tungstophosphoric acid (Cu-TPA) as a heterogeneous catalyst [11]. This method offers significant advantages such as high conversions, mild conditions, ease of recovery, and reusability of the catalyst, which renders it a useful and attractive procedure for the synthesis of 2,3,4,5-tetrahydro-4-methylidenefuran derivatives **3**.

Experimental Part

General. M.p.: determined in open cap. tubes in H$_2$SO$_4$ bath; uncorrected. TLC: SiO$_2$; visualization with I$_2$ or UV light. IR Spectra: *Perkin-Elmer 1000* instrument; in KBr pellets. ^{1}H-NMR Spectra: *Bruker 300* MHz spectrometer; in CDCl$_3$ or (D$_6$)DMSO; with TMS as internal standard. MS: *Waters ZQ Micromass* LC-MS spectrometer.

General Procedure. To a stirred soln. of 2-(arylmethylidene)propane-1,3-dinitrile **1** (1 mmol), propargyl alcohol (**2**; 1.2 mmol) in MeCN (5 ml) was added EtN(^{i}Pr)$_2$ (2 mmol) and Cu-TPA (10 mol-%). The mixture was stirred at r.t. for appropriate time. After completion of the reaction (TLC), the mixture was diluted with H$_2$O (10 ml) and extracted with AcOEt (3 × 15 ml), dried (Na$_2$SO$_4$), and concentrated in vacuum to give the crude product, which was charged on small SiO$_2$ column and eluted with AcOEt/hexane 1:9 to afford pure product **3**. The structures of products were established by comparing their NMR, IR, and mass spectra with those of the authentic compounds.

*4,5-Dihydro-4-methylidene-2-phenylfuran-3,3(2*H*)-dicarbonitrile* (**3a**). White solid. M.p. 119°. IR (KBr): 3032, 2924, 2869, 2230, 1593, 1454, 1217, 1064, 756, 723. ^{1}H-NMR (300 MHz, CDCl$_3$): 7.40–7.65 (*m*, 5 H); 5.88–5.81 (*m*, 1 H); 5.64–5.57 (*m*, 1 H); 5.10 (*s*, 1 H); 4.9 (*dt*, *J* = 2.2, 13.5, 1 H); 4.65 (*dt*, *J* = 2.2, 13.5, 1 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 36.5; 46.3; 70.0; 87.2; 111.5; 114.4; 126.2; 128.5; 129.5; 130.7; 132.5; 142. EI-MS: 210 (*M*$^+$).

*2-(4-Bromophenyl)-4,5-dihydro-4-methylidenefuran-3,3(2*H*)-dicarbonitrile* (**3c**). Light-yellow solid. M.p. 96°. IR (KBr): 3021, 2977, 2873, 2361, 1585, 1490, 1216, 1073, 759, 669. ^{1}H-NMR (200 MHz, CDCl$_3$): 7.65 (*d*, *J* = 8.5, 2 H); 7.4 (*d*, *J* = 8.5, 2 H); 5.88–5.81 (*m*, 1 H); 5.63–5.56 (*m*, 1 H); 5.51 (*s*, 1 H); 4.90 (*dt*, *J* = 2.3, 13.2, 1 H); 4.6 (*dt*, *J* = 2.3, 13.9, 1 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 46; 71; 87; 111; 113; 115; 128; 131; 132; 133; 137; 158. EI-MS: 288 (*M*$^+$).

*4,5-Dihydro-4-methylidene-2-(3-nitrophenyl)furan-3,3(2*H*)-dicarbonitrile* (**3g**). White solid. M.p. 136°. IR (KBr): 3023, 2928, 1527, 1349, 1216, 1071, 757. ^{1}H-NMR (300 MHz, CDCl$_3$): 8.45 (*s*, 1 H); 8.35 (*d*, *J* = 8.3, 1 H); 7.9 (*d*, *J* = 6.7, 1 H); 7.75 (*t*, *J* = 7.5, 1 H); 5.95–5.88 (*m*, 1 H); 5.69–5.62 (*m*, 1 H); 5.22 (*s*, 1 H); 4.93 (*d*, *J* = 14.3, 1 H); 4.7 (*d*, *J* = 14.3, 1 H). ^{13}C-NMR (75 MHz, CDCl$_3$): 46; 70; 86; 111; 112.5; 115.2; 121.8; 125; 130.2; 132; 135; 141; 148.5. EI-MS: 255 (*M*$^+$).

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