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Convenient Synthesis of 3-Cyano-4,5-dihydrofurans and 4-Cyano-1,2-dioxan-3-ols Using Acylacetonitrile Building Block

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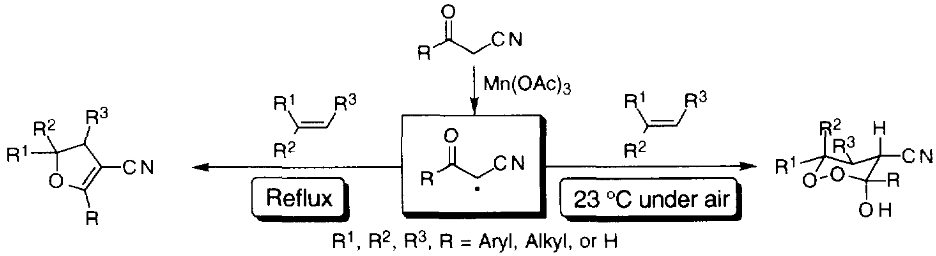
Abstract: Acylacetonitriles were easily oxidized with manganese(III) acetate in acetic acid to form the corresponding acylcyanomethyl radicals, which attacked alkenes at reflux temperature to give new 3-cyano-4,5-dihydrofurans and at the room temperature under air to yield new 4-cyano-1,2-dioxan-3-ols in good yields.

Acylacetonitriles have been used as a building block for the syntheses of 4*H*-pyrans,[1] 2-pyridones,[2] and furans.[3] During the first step in these syntheses, α-acylcinnamonitriles were prepared by Knoevenagel condensation of aldehydes and acylacetonitriles, followed by Michael addition of malononitrile or malonamide and nucleophilic intramolecular cyclization for the final step to give the corresponding heterocyclic compounds. Because α-protons of the acylacetonitriles are more acidic than those of the methyl ketones, we thought that acylacetonitriles must be quite sensitive to a metal oxidant such as manganese(III) acetate similar to 1,3-dicarbonyl compounds.[4] The reactivity of the enolizable methyl ketone itself to manganese(III) acetate is not very high, and sometimes manganese(III) oxidation needs a co-oxidant such as copper(II) acetate.[5] Although the manganese(III) acetate oxidation of acetophenone in the presence of alkenes does give the corresponding tetralones, the product yields are not satisfactory.[6] On the other hand, it is known that α-cyanoacetic acid was used in the manganese(III) oxidation system in order to synthesize α-substituted γ-lactones.[7] Fristad et al. reported that α-cyanoacetic acid was oxidized 3×10^5 times faster than acetic acid based on the α-hydrogen acidity.[7b,c] Therefore, we expected that acylcyanomethyl radicals would be similarly formed by the interaction of acylacetonitrile and manganese(III) acetate because the α-protons of the acylacetonitrile are activated by the cyano group and the acyl group. If the acylcyanomethyl radicals would be formed in the manganese(III) oxidation system, the radicals must attack alkenes to give heterocyclic compounds in one step.[8] In fact, the reaction of 1,1-diphenylethene at reflux temperature gave new 5,5-diphenyl-3-cyano-4,5-dihydrofurans, and a similar reaction at 23 °C under dry air yielded new 6,6-diphenyl-4-cyano-1,2-dioxan-3-ols. Herein we briefly report the results of our study.

1,1-Diphenylethene (1 mmol) and benzoylacetonitrile (2 mmol) were dissolved in hot acetic acid (15 mL), and manganese(III) acetate (3 mmol) was added to the hot acetic acid solution just before refluxing. The mixture was refluxed until the dark brown color of the solution turned transparent yellow (normally for 1 min). The solvent was removed and the residue was treated with water (30 mL). Extraction of the aqueous solution

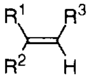
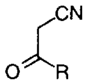
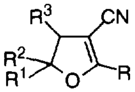
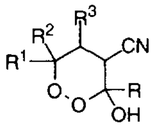
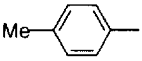
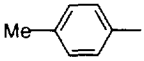
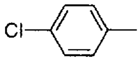
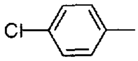
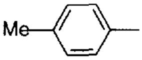
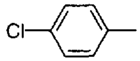
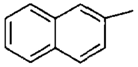
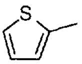
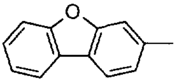
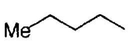


with chloroform and then silica-gel TLC separation using chloroform gave 3-cyano-2,5,5-triphenyl-4,5-dihydrofuran in 65% yield. This fact definitely shows the formation of acylcyanomethyl radicals. We therefore prepared other acylacetonitriles by bromination of the corresponding methyl ketones followed by cyanidation[9] and allowed the reaction to occur under similar conditions. After the usual work-up, we obtained the corresponding 3-cyano-5,5-diphenyl-4,5-dihydrofurans in good yields as shown in Table 1.[10] Using 1,1-diarylethenes having an electron-donating group on the aryl rings such as 1,1-bis(4-methylphenyl)ethene under similar reaction conditions increased the yield of the corresponding dihydrofuran (86% yield). This is due to the facility of oxidation of the secondary alkyl radical formed by the addition of an acylcyanomethyl radical to the alkene.[11] In addition, using acylacetonitrile having an electron-withdrawing group on the aryl ring such as (4-chlorobenzoyl)acetonitrile also increased the yield of the corresponding dihydrofuran. For example, the reaction of 1,1-diphenylethene with (4-methylbenzoyl)acetonitrile afforded 3-cyano-2-(4-methylphenyl)-5,5-diphenyl-4,5-dihydrofuran in 67% yield, while a similar reaction with (4-chlorobenzoyl)acetonitrile gave 2-(4-chlorophenyl)-3-cyano-5,5-diphenyl-4,5-dihydrofuran in 74% yield. The rate of oxidation of the acylacetonitrile is expected to increase with increasing enolizability, or the acidity of an α-proton, of the carbonyl compound being oxidized with manganese(III) acetate.[7b]

On the other hand, a mixture of 1,1-diphenylethene (1 mmol), benzoylacetonitrile (2 mmol), and manganese(III) acetate (0.5 mmol) was stirred in acetic acid (15 mL) at 23 °C under bubbling dry air until the dark brown color of the solution turned colorless (normally for 3 h). The usual work-up was done and 4-cyano-3,6,6-triphenyl-1,2-dioxan-3-ol was obtained in 86% yield.[12] A similar substituent effect for the ethenes and acylacetonitriles was observed, and the yields of the corresponding 4-cyano-1,2-dioxan-3-ols increased. For example, the reaction of 1,1-bis(4-methoxyphenyl)ethene with benzoylacetonitrile gave 4-cyano-3-hydroxy-6,6-bis(4-methoxyphenyl)-4-phenyl-1,2-dioxan-3-ol in 92% yield, while using (4-chlorobenzoyl)acetonitrile in the case of 1,1-diphenylethene led to 3-(4-chlorophenyl)-4-cyano-3-hydroxy-6,6-diphenyl-1,2-dioxan-3-ol in 92% yield. The reaction of 2-phenylpropene, *trans*-stilbene, 2-methylpropene or cyclooctene gave the corresponding 1,2-dioxan-3-ols in moderate yields. The use of acylacetonitriles having alkyl, aryl, and heterocyclic groups also led to good results as shown in Table 1.

Both reactions formed only the desired heterocyclic compounds in one step and no other by-products were isolated. Accordingly, we guarantee that the present reactions are the most convenient selective synthetic method of preparing 3-cyano-4,5-dihydrofurans and 4-cyano-1,2-dioxan-3-ols. In addition, although the 1,2-dioxane ring is easily decomposed in the presence of a strong acid catalyst which converts to a furan ring,[13] we believe that the cyano group bearing a dihydrofuran ring and a 1,2-dioxane ring can be transferred to other functional groups.

Table 1. Reaction of Ethenes with Acylacetonitriles in the Presence of Manganese(III) Acetate

Alkene			Acylacetonitrile	Product (yield / %)[a]	
					
R^1	R^2	R^3	R	4,5-Dihydrofuran[b]	1,2-Dioxan-3-ol[c]
Ph	Ph	H	Ph	65	86
		H	Ph	86	88
		H	Ph	59	80
Me	Ph	H	Ph	25	61
H	Ph	Ph	Ph	34	13
Me	Me	H	Ph	4	41
—$(CH_2)_6$—R^3	H		Ph	6	25
Ph	Ph	H		67	86
Ph	Ph	H		74	92
Ph	Ph	H		68	91
Ph	Ph	H		88	72
Ph	Ph	H		70	80
Ph	Ph	H		59	92

[a] Isolated yields based on the amount of the ethene used. [b] The reaction was carried out at the reflux temperature except for the reaction of 2-methylpropene (80 °C). [c] The reaction was carried out at 23 °C under dry air.

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References and Notes

1. (a) Quinterio, M.; Seoane, C.; Soto, J. L. *Tetrahedron Lett.* **1977**, *18*, 1835. (b) Quinterio, M.; Soto, J. L. *J. Heterocyclic Chem.* **1978**, *15*, 57. (c) Soto, J. L.; Seoane, C.; Martin, N.; Quinterio, M. *Heterocycles*, **1984**, *22*, 1.
2. (a) Seoane, C.; Soto, J. L.; Zamorano, M. P. *Heterocycles*, **1980**, *14*, 639. (b) Martin, N.; Seoane, C.; Soto, J. L. *Heterocycles*, **1985**, *23*, 2013. (c) Soto, J. L.; Seoane, C.; Zamorano, P.; Rubio, M. J.; Monforte, A.; Quinterio, M. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1681.
3. (a) Aran, V. J.; Soto, J. L. *Synthesis*, **1982**, 513. (b) Ciller, J. A.; Martin, N.; Seoane, C.; Soto, J. L. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2581.
4. Nishino, H.; Kamachi, H.; Baba, H.; Kurosawa, K. *J. Org. Chem.* **1992**, *57*, 3551.
5. (a) Heiba, E. I.: Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524. (b) Kurz, M. E.; Baru, V.; Nguyen, P.-N. *J. Org. Chem.* **1984**, *49*, 1603. (c) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607.
6. Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 2888.
7. (a) Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977. (b) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10. (c) Fristad, W. E.; Peterson, J. R.; Ernst, A. B. *J. Org. Chem.* **1985**, *50*, 3143. (d) Ernst, A. B.; Fristad, W. E. *Tetrahedron Lett.* **1985**, *26*, 3761. (e) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1985**, *26*, 4291.
8. (a) Nishino, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1922. (b) Nishino, H.; Tategami, S.; Yamada, T.; Korp, J. D.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1800.
9. (a) Long, R. S. *J. Am. Chem. Soc.* **1947**, *69*, 990. (b) Friedman, L.; Shechter, H. *J. Org. Chem.* **1960**, *25*, 877. (c) Gaudry, M.; Marquet, A. *Tetrahedron*, **1970**, *26*, 5611; *ibid*, **1970**, *26*, 5617. (d) Prakash, O.; Tomer, R. K.; Kodali, D. R. *J. Indian Chem. Soc.* **1978**, *LV*, 919.
10. The structures of the obtained 3-cyano-4,5-dihydrofurans were determined by spectrophotometric methods and combustion analyses. For example, 3-cyano-2,5,5-triphenyl-4,5-dihydrofuran: Colorless microcrystals (from $CHCl_3$/hexane); mp 142 °C; IR ($CHCl_3$) ν 2196 (CN); ^1H NMR ($CDCl_3$) δ 3.7 (2H, s, CH_2), 7.3-8.3 (15H, m, arom H); ^{13}C NMR ($CDCl_3$) δ 165.3 (C-2), 143.9, 127.9 (arom C), 131.5, 128.8, 128.6, 128.0, 127.2, 125.6 (arom CH), 117.3 (CN), 92.9 (C-3), 79.1 (C-5), 45.6 (CH_2); MS *m/z* (rel intensity), 323 (M^+, 47), 207 (10), 165 (18), 105 (100), and 77 (84). Anal. Calcd for $C_{23}H_{17}ON$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.64; H, 5.30; N, 4.33.
11. Nishino, H.; Hashimoto, H.; Korp. J. D.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1999.
12. The structure of 4-cyano-3,6,6-triphenyl-1,2-dioxan-3-ol was supported by all of the spectral data and elemental analyses: Colorless microcrystals (from $CHCl_3$); mp 178 °C; IR ($CHCl_3$) ν 3600-3100 (OH), 2253 (CN); ^1H NMR ($CDCl_3$) δ 3.3 (3H, s, CH_2CH), 4.0 (1H, bs, OH), 7.3-7.8 (15H, m, arom H); ^{13}C NMR ($CDCl_3$) δ 141.5, 139.2, 137.7 (arom C), 130.0, 128.9, 128.74, 128.68, 128.6, 128.1, 126.9, 126.2, 125.5 (arom CH), 117.8 (CN), 98.2 (C-3), 85.5 (C-6), 35.6 (CH), and 33.0 (CH_2). Anal. Calcd for $C_{23}H_{19}O_3N$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.58; H, 5.40; N, 3.90.
13. (a) Qian, C.-Y.; Yamada, T.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1371. (b) Qian, C.-Y.; Hirose, J.; Nishino, H.; Kurosawa, K. *J. Heterocyclic Chem.* **1994**, *31*, 1219.

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