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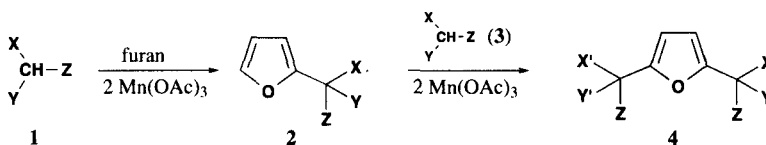
2,5-DISUBSTITUTED FURANS BY OXIDATION OF β -DICARBONYL COMPOUNDS IN THE PRESENCE OF FURAN

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The oxidation of C-H active substrates by high valent metal salts in the presence of aromatic substrates provides a powerful approach to arylmethyl derivatives through homolytic aromatic substitution.¹ However, the synthetic potential of these radical sources toward polysubstitution has been investigated only sporadically. We now report examples of an efficient and selective 2,5-difunctionalization of furan by oxidation of β -dicarbonyl derivatives **1a-f** with Mn(III) acetate. The results also help define the limits and potentiality of the process, provided efficient monosubstitution is attained.



- a) X = Me, Y = Z = CO₂Et
 b) X = Bn, Y = Z = CO₂Et
 c) X = Me, Y = COMe, Z = CO₂Et
 d) X = Y = Z = CO₂Et
 e) X = CH(CO₂Et)₂, Y = Z = CO₂Et
 f) X = NHCHO, Y = Z = CO₂Et

- a) X = X' = Me, Y = Y' = Z = CO₂Et
 b) X = X' = Bn, Y = Y' = Z = CO₂Et
 c) X = Me, X' = Bn, Y = Y' = Z = CO₂Et
 d) X = X' = Me, Y = COMe, Y' = Z = CO₂Et
 e) X = X' = Y = Y' = Z = CO₂Et
 f) X = X' = NHCHO, Y = Y' = Z = CO₂Et

Intramolecular 1,5- or 1,6-annulation are efficient processes in C-H active substrates substituted by a γ -arylalkyl group² or in tandem addition to double or triple bonds,^{3,4} however, intermolecular substitutions are synthetically less useful because of low positional and substrate selectivity.⁵ The best results are obtained with electron-rich aromatic rings, advantage being taken of the reactivity of the intermediate electrophilic radicals.³ Furan, thiophene and pyrrole derivatives owing to their diene-like structure, afford at low conversion, selective substitution at position 2 by a variety of carbon-centered radicals.⁶ Studies of these last processes allowed us to develop mild and convenient one-pot procedures (procedures A and C or B and C) to obtain symmetric and asymmetric 2,5-disubstituted furans. Table 1 summarizes some representative data of yield of isolated **4**. Procedures A and B provide high yields of **2** at low conversion of furan (< 50%) (procedure B in particular uses furan as solvent in the presence of 10% acetic acid).

Under these conditions, no polymerization or oxidation of furan occurs and β -dicarbonyl derivatives which are not very reactive towards the aromatic substrate, such as β -ketoester **1c** and amidoester **1f**, react efficiently with furan. The disubstituted products **4** were obtained by removing excess furan from the crude mixture obtained from procedure A or B, adding the carbonyl compound

(1 or 3), $\text{Mn}(\text{OAc})_3$ and acetic acid and heating the resulting mixture at 70° for 6-10 h (procedure C). Despite the mildness and convenience of this methodology, some limits are evident. Thus, highly stabilized radicals⁷ generated from β -ketoesters **1c** afford only traces of **4g** ($X = X' = \text{Me}$, $Y = Y' = \text{COMe}$, $Z = \text{CO}_2\text{Et}$), but are sufficiently reactive towards derivative **2a** to give the unsymmetrical product **4d**. The order of addition of reagents is important: for example, **4d** is formed only in trace quantity by an inverse sequence. The high reactivity of compound **2c** towards $\text{Mn}(\text{III})$ prevents further substitutions. Similarly polysubstitution cannot be cleanly obtained with diethyl malonate, ethyl acetoacetate, diethyl chloromalonate and ethyl chloroacetate despite the high reactivity of the corresponding radicals towards furan, owing to the rapid side chain oxidation of the monoaddition product **2** with the first two substrates and to the hydrolysis of the benzylic chloro substituents with the latter two substrates.⁸

TABLE 1. Yield and Physical Constants of Compounds **2** and **4**

Compd	Yield (%)	mp. (or bp.) ($^\circ\text{C}$)/torr	Procedure	Elemental Analyses (Found)	
				C	H
2a	73 ^a	90-91/0.7	A	59.99 (60.13)	6.71 (6.90)
2b	69 ^b	57-58	A	68.34 (68.28)	6.37 (6.51)
2c	78	82-84/1	B	62.85 (63.04)	6.71 (6.44)
2d	81 ^c	134-136/0.01	A	56.37 (56.28)	6.08 (6.12)
2e	71	147-149/0.01	A	56.25 (56.31)	6.29 (6.35)
4a	83	171-172/0.7	A/C	58.24 (58.41)	6.84 (6.94)
4b	60	65-66	A/C	68.07 (68.14)	6.43 (6.53)
4c	69 ^d	181-183/0.01	A/C	63.92 (64.11)	6.60 (6.73)
4d	65	oil ^c	B/C	59.68 (59.83)	6.85 (6.94)
4e	74	53-54	A/C	54.54 (54.41)	6.10 (6.22)
4f	55	102-103	B/C	51.06 (50.94)	5.57 (5.47)

a) Compound **4a** (5%) was also formed. b) Compound **4b** (18%) was also formed. c) Compound **4e** (< 5%) was also formed. d) Compound **4b** (12%) was also formed. e) Decomposes on heating.

EXPERIMENTAL SECTION

Mps were determined using a Büchi 510 apparatus and are uncorrected. ^1H NMR spectra were obtained on a Bruker AC-250 MHz spectrometer with chemical shifts (δ) given in ppm from internal TMS reference (in CDCl_3). Low resolution electron impact mass spectra (MS) were recorded on a Finnigan TSQ-70 mass spectrometer. Microanalysis were performed by Redox Laboratory (Milan).

General Procedures. Method A. - The carbonyl compound (6.0 mmol) and furan (5 mL) were added to a cold (10 - 15°) solution of $\text{Mn}(\text{OAc})_3 \cdot 2 \text{H}_2\text{O}$ (12.6 mmol) in AcOH (40 mL) in a 50-mL borosilicate Wheaton round bottom flask with screw-treated connections. The cup was firmly tightened and

TABLE 2. ¹H NMR and MS Spectral Data of Compounds 2 and 4

Compd.	¹ H NMR (δ)	MS (m/e) (rel int.%)
2a	1.26 (6H, t), 1.63 (3H, s), 4.24 (4H, q), 6.36 (2H, t, H ₃), 7.40 (1H, t, H ₂).	240 (M ⁺ , 20), 167 (100), 139 (40), 129 (30), 121 (30), 111 (15), 93 (50), 74 (25), 66 (10)
2b	1.22 (6H, t), 3.62 (2H, s), 4.24 (4H, q), 6.34 (1H, dd, J = 3 and 1.8 Hz, H ₃), 6.55 (1H, dd, J = 3 and 0.9 Hz, H ₄), 6.75-6.81 (2H, m), 7.1-7.18 (3H, m), 7.42 (1H, dd, J = 1.9 and 0.9 Hz, H ₅)	316 (M ⁺ , 33), 270 (5), 243 (15), 225 (68), 180 (30), 153 (25), 141 (15), 91 (100), 43 (40)
2c	1.29 (3H, t), 1.72 (3H, s), 2.25 (3H, s.), 4.25 (2H, q), 6.38-6.41 (2H, m, H _{3,4}), 7.42 (1H, t, H ₂)	210 (M ⁺ , 0.5), 168 (100), 139 (70), 134 (12), 121 (30), 93 (60), 66 (30)
2d	1.3 (9H, t), 4.32 (6H, q), 6.38 (1H, J _{ab} = 3 Hz, J _{ax} = 1.8 Hz, H ₄), 6.72 (1H, J _{ab} = 3 Hz, J _{bx} = 0.9 Hz, H ₃), 7.45 (1H, X of ABX, J _{ax} = 1.8 Hz, J _{bx} = 0.9 Hz, H ₅)	298 (M ⁺ , 8), 254 (2), 255 (30), 226 (7), 181 (11), 180 (100), 153 (21), 153 (21), 108 (27), 107 (20), 95 (22)
2e	1.26 (12H, t), 4.21 (4H, q), 4.29 (4H, q), 4.57 (1H, s), 6.37 (1H, J = 3.6 and 1.8 Hz), 6.44 (1H, J = 3.6 and 0.9 Hz), 7.37 (1H, J = 1.8 and 0.9 Hz).	384 (M ⁺ , 12), 311 (24), 294 (11), 266 (49), 238 (43), 220 (22), 193 (70), 191 (17), 165 (100), 137 (38), 95 (15)
4a	1.25 (12H, q), 1.8 (6H, s), 4.23 (8H, t), 6.34 (2H, s, H ₃)	412 (M ⁺ , 15), 339 (100), 294 (15), 267 (25), 221 (60), 194 (20), 117 (10), 93 (15), 43 (40)
4b	1.24 and 1.28 (12H, 2t), 3.35 (2H, s), 3.61 (2H, s), 4.24 (8H, q), 6.51 (2H, s, H _{3,4}), 6.7-6.8 (4H, m), 7.1-7.2 (6H, m)	564 (M ⁺ , 10), 427 (100), 353 (18), 338 (15), 249 (15), 91 (30)
4c	1.22 (6H, t), 1.26 (6H, t), 1.8 (3H, s), 3.6 (2H, s), 4.18 (4H, q), 4.24 (4H, q), 6.30 and 6.52 (2H, 2d, J = 3.5 Hz, H ₃ -H ₄), 6.75-6.85 (2H, m), 7.1-7.25 (3H, m)	488 (M ⁺ , 18), 415 (18), 398 (10), 397 (77), 369 (8), 297 (12), 280 (13), 279 (100), 269 (15), 203 (8), 91 (18)
4d	1.2-1.35 (12H, m), 1.68 (3H, s), 1.81 (3H, s), 2.15 (3H, s), 4.1-4.3 (6H, m), 6.35 (2H, s, H _{3,4})	382 (M ⁺ , 5), 340 (20), 339 (23), 294 (100), 267 (25), 221 (90), 193 (15), 174 (13), 155 (45), 127 (45), 93 (12)
4e	1.29 (18H, t), 4.3 (12H, q), 6.7 (2H, s)	528 (M ⁺ , 0.3), 411 (6), 410 (29), 338 (16), 337 (100), 292 (43), 147 (20).
4f	1.29 (18H, t), 4.3 (12H, q), 6.6 (2H, s), 7.3 (2H, s br.), 8.1 (2H, d, J = 1.5 Hz)	470 (M ⁺ , 2), 397 (8), 370 (60), 341 (41), 196 (20), 168 (71), 151 (44), 140 (100), 94 (71).

the flash was placed in a thermostated bath at $70 \pm 1^\circ$ for 8 h with magnetic stirring. To recover furan 2, the reaction mixture was cooled, diluted with water (25 mL) and extracted with ether (4x20 mL). The combined ethereal extracts were washed with 15% Na₂CO₃ until neutral and water (10 mL), then dried on Na₂SO₄ and the residue distilled or flash chromatographed on SiO₂ (eluent: pentane/ether,

gradient from 95:5 to 80:20).

Method B.- The reaction was carried out as in method A, by using furan and AcOH (9:1 w/w, 26 g) as solvent. The heterogeneous mixture was heated in a 35 mL screw cap Wheaton flash at 70° for 6 h, then furan was recovered by distillation. Compound **2** was purified by taking up the residue in pentane or ether (3x10 mL) and flash chromatography on SiO₂ (eluent: pentane/ether 8:2).

Method C.- The reaction mixture obtained by procedure A or B was cooled at 40° and the excess furan was eliminated by flushing with N₂ for 0.5 h (vapor trap at -78°). Then, carbonyl compound **3** (6 mmol) and Mn(OAc)₃ (15.0 mmol) were added, the bottle rinsed and heated at 70-80° for 4-6 h. The solvent was distilled (5 torr) and the residue was taken up with H₂O and EtOAc (1:1, 30 mL), the phases were separated and the water were extracted with EtOAc (2 x 10 mL). The combined extracts were washed with 10% NaHCO₃, dried, concentrated and the residue distilled or flash chromatographed.

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REFERENCES

1. a) A. Citterio and R. Santi, *NATO-Asi Ser. C*, 187 (1989); b) R. Santi; F. Bergamini, A. Citterio, R. Sebastiano and M. Nicolini, *J. Org. Chem.*, **57**, 4250 (1992); c) B. B. Snider, R. Mohan and S. A. Kates, *J. Org. Chem.*, **50**, 3659 (1985); c) G. G. Melikyan, *Synthesis*, 833 (1993).
2. a) A. Citterio and R. Santi, *J. Org. Chem.*, **54**, 2703 (1989); b) A. Citterio, S. Cardani, R. Sebastiano and M. Nicolini, *Gazz. Chim. Ital.*, **123**, 1035 (1993).
3. a) A. Citterio, R. Sebastiano, A. Marion and R. Santi, *J. Org. Chem.*, **56**, 5328, (1991).
4. a) B. B. Snider, R. Mohan and S. A. Kates, *Tetrahedron Lett.*, 841 (1987).
5. a) A. Citterio, D. Fancelli, C. Finzi, L. Pesce and R. Santi, *J. Org. Chem.*, **54**, 2713 (1989); b) H. Nishino, K. Tsunoda and K. Kurosawa, *Bull. Chem. Soc. Jpn.*, **62**, 545 (1989).
6. a) G.I. Nikishin, *Bull. Acad. Sci. USSR*, **33**, 109 (1984); b) L. W. Weinstock, E. Corley, N. L. Abramson, A. O. King and S. Karady, *Heterocycles*, **27**, 2627 (1988); c) I. S. Cho and J. M. Muchowski, *Synthesis*, 567 (1991); d) E. Baciocchi, E. Muraglia and G. Sleiter, *J. Org. Chem.*, **57**, 6817 (1992).
7. a) H. Birkhofer, J. Hadrich, J. Pakusch, H.-D. Beckhaus, C. Ruchardt, K. Peters and H.-G. v. Schnering *NATO-Asi Ser. C*, 260, 27 (1989); b) R. Schulze, H.-D. Beckhaus and C. Ruchardt, *Chem. Ber.*, **126**, 1031 (1993).
8. a) F. Bergamini, N. Gatti, R. Santi, A. Citterio, M. Nicolini and R. Sebastiano, *J. Chem. Res. (S)* 364, (M) 2455 (1993); b) ref. 1a, p. 197.
