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Tetrahedron Letters 45 (2004) 5743–5745
Tetrahedron Letters

An innovative approach to the synthesis of substituted benzaldehydes through carbanion induced ring transformation of suitably functionalized 2*H*-pyran-2-ones ☆

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Received 23 March 2004; revised 6 May 2004; accepted 14 May 2004
Available online 11 June 2004

Abstract—An innovative route for the synthesis of substituted benzaldehydes has been delineated through a ring transformation reaction of suitably functionalized 2*H*-pyran-2-ones by methylglyoxaldimethylacetal followed by Amberlyst 15 or acid catalyzed cleavage of the intermediate acetal in good yield.

The versatility of the formyl group for generating molecular diversity through C–C and C–heteroatom bond formation[1] is widely recognized. Formyl derivatives are widely used as ligands for the synthesis of metal chelates. The synthesis of formylbiaryls and formylaryl–heteroaryls is of significant importance as they are useful building blocks for the construction of various synthetic and natural products.

The formyl group is generally introduced to aromatic systems by Gatterman,[2] Gatterman–Koch,[3] and Vilsmeier–Haack[4] reactions and also by formylation with orthoformate,[5] formyl fluoride–BF_3[6] and dichloromethyl methyl ether–$AlCl_3$.[7] Besides these methods they are also prepared by oxidation of methyl or hydroxymethyl arenes[8] and by reduction of nitriles,[9] amides[10] and acid chlorides.[11] The wide-ranging applications and limitations of existing procedures prompted us to develop a novel route to the synthesis of highly functionalized substituted benzaldehydes. Recently, Junjappa and co-workers[1] reported the synthesis of formyl heteroarenes through heterocyclization of 1-bis(methoxy)-4-bis(methylthio)-3-butene-2-one. We now report an innovative synthesis of substituted benzaldehydes through ring transformation of suitably functionalized 2*H*-pyran-2-ones **1** by methylglyoxaldimethylacetal **2** to masked substituted benzaldehydes **3** followed by either Amberlyst 15 or acid catalyzed acetal cleavage to yield substituted benzaldehydes **4**.

6-Aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile **1a**,[12] 6-aryl-4-piperidin-1-yl-2*H*-pyran-2-one-3-carbonitrile **1b**,[13] 6-aryl-4-pyrrolidin-1-yl-*2H*-pyran-2-one-3-carbonitrile **1c**[13] and methyl 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carboxylate **1d**,[14] were obtained from the reaction of aryl methyl ketones and ketene dithioacetal, the cyclic aminals **1b**,**c** being prepared on further reaction of the 6-aryl-4-methyl-sulfanyl-*2H*-pyran-2-one-3-carbonitrile **1a** with piperidine and pyrrolidine in refluxing methanol and isolated as usual. These lactones **1a**–**d** were used as precursors for carbanion induced ring transformation reactions, using methylglyoxaldimethylacetal **2** as carbanion source, generated in situ by the action of powdered KOH in DMF.

The topography of the 2*H*-pyran-2-ones **1** is such that they can be considered as cyclic ketene hemithioacetals **1a**,**d** and cyclic ketene hemiaminals **1b**,**c**, C-6 of which is highly susceptible to nucleophilic attack due to extended conjugation and the presence of the an electron withdrawing substituent at position 3 of the pyran ring. Masked substituted benzaldehydes were synthesized by stirring an equimolar mixture of **1**, methylglyoxaldimethylacetal **2** and powdered KOH in dry DMF at room temperature for 24 h, followed by pouring onto crushed ice with vigorous stirring for 1 h whilst maintaining a neutral pH by adding 10% aqueous HCl. The

☆ Communication No. 6546.

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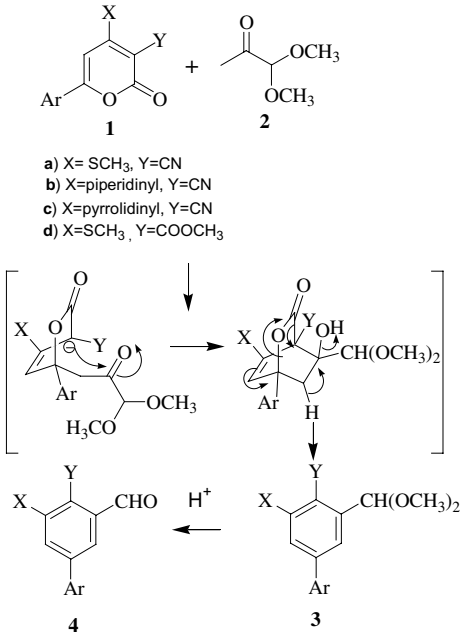
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.05.095

precipitate obtained was filtered, washed with water and finally the crude product was purified on a Si gel column to afford the masked substituted benzaldehydes **3** as viscous liquids or low melting solids. Hydrolysis either by stirring with Amberlyst 15 in chloroform or refluxing with 4% ethanolic HCl gave the corresponding substituted benzaldehydes **4**. The Amberlyst 15 catalyzed acetal hydrolysis of the masked substituted benzaldehydes **3** was found to be a high yielding, cleaner, reaction compared to the acid catalyzed reaction (40–65% yields).

The reaction is possibly initiated by attack of the carbanion generated in situ from methylglyoxaldimethylacetal **2** at C-6 with ring-closing followed by decarboxylation and dehydration to yield **3**, which on acetal hydrolysis by Amberlyst 15 or ethanolic-HCl (4%) led to the substituted benzaldehydes **4**. The synthetic strategy followed is far superior to known procedures with respect to ease of work-up, mild reaction conditions and cost effectiveness (Table 1).



Scheme 1.

Table 1. Derivatives of **3** and **4** produced according to Scheme 1

3, 4	Ar	X	Y	Yield (%)	
				3	4
a	C_6H_5	SCH_3	CN	62	95
b	C_6H_5	Piperidinyl	CN	59	90
c	4-FC_6H_4	SCH_3	CN	25	91
d	4-ClC_6H_4	Pyrrolidinyl	CN	50	90
e	4-BrC_6H_4	SCH_3	CN	46	95
f	4-$CH_3SC_6H_4$	SCH_3	CN	21	96
g	4-$CH_3C_6H_4$	SCH_3	CN	50	94
h	$C_{10}H_7$	SCH_3	CN	38	93
i	$C_{10}H_7$	SCH_3	CO_2Me	36	—
j	$C_{10}H_7$	Piperidinyl	CN	52	90
k	Thienyl	SCH_3	CN	41	92

All the compounds synthesized were characterized by elemental and spectroscopic analyses.[15] This methodology provides a novel route for the synthesis of a wide variety of highly functionalized substituted benzaldehydes in high yield and in only two steps.

Acknowledgements

D.S. is grateful to CSIR for a senior research fellowship. The authors are also thankful to SAIF, Central Drug Research Institute, Lucknow for providing spectroscopic data and elemental analyses for the synthesized compounds.

References and notes

1. Mohata, P. K.; Kumar, U. K. S.; Sriram, V.; Illa, H.; Junjappa, H. *Tetrahedron* **2003**, *59*, 2631.
2. (a) Truce, W. E. *Org. React.* **1957**, *9*, 37; (b) Tanaka, M.; Fujiwara, M.; Ando, H. *J. Org. Chem.* **1995**, *60*, 2106; (c) Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 691.
3. (a) Toniolo, L.; Graziani, M. *J. Organomet. Chem.* **1980**, *194*, 221; (b) Grounse, N. N. *Org. React.* **1949**, *5*, 290.
4. (a) Blaser, D.; Calmes, M.; Daunis, J.; Natt, F.; Tardy-Delassus, A.; Jacquier, R. *Org. Prep. Proced. Int.* **1993**, *25*, 338; (b) Jutz, C. *Adv. Org. Chem.* **1976**, *9*, 225; (c) Meth-Cohn, O.; Goon, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 85; (d) Kantlehner, W. *Adv. Org. Chem.* **1979**, *9*, 5; (e) Meth-Cohn, O.; Tarnowski, B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1982; Vol. 31, pp 207–236; (f) Rudloff, I.; Michalik, M.; Montero, A.; Peseke, K. *Synthesis* **2001**, 1686.
5. Gross, S.; Rieche, A.; Matthey, G. *Chem. Ber.* **1963**, *96*, 308.
6. Olah, G. A.; Kuhn, S. J. *J. Am. Chem. Soc.* **1960**, *82*, 2380.
7. (a) Reiche, A.; Gross, H.; Hoft, E. *Chem. Ber.* **1960**, *93*, 88; (b) Lewin, A. H.; Parker, S. R.; Fleming, N. B.; Carrol, F. I. *Org. Prep. Proced. Int.* **1978**, *10*, 201.
8. Frey, L. F.; Marcantonio, K.; Frantz, D. E.; Murry, J. A.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6815.
9. Zil'berman, E. N.; Pyryalova, P. S. *J. Gen. Chem. USSR* **1963**, *33*, 3348.
10. (a) Zakharkin, L. I.; Khorlina, I. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1959**, 2046; (b) Muraki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 875; (c) Godjoian, G.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 1717.
11. (a) Cha, J. S.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 4732; (b) Maier, W. F.; Chettle, S. J.; Rai, R. S.; Thomas, G. *J. Am. Chem. Soc.* **1986**, *108*, 2608.
12. (a) Ram, V. J.; Haque, N.; Singh, S. K.; Hussaini, F. A.; Shoeb, A. *Indian J. Chem.* **1993**, *32B*, 1993; (b) Tominaga, Y.; Ushirogochi, A.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 3395.
13. (a) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *Liebigs Ann. Chem.* **1991**, 1229; (b) Ram, V. J.; Nath, M.; Srivastava, P.; Sarkhel, S.; Maulik, P. *J. Chem. Soc.* **2000**, 3719.
14. (a) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *J. Chem. Res. (S)* **1991**, 98; (b) Tominaga, Y.; Ushirogo-

chi, A.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 1557.

15. *Typical procedure*: *Compound* **3a**: A mixture of 6-phenyl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitrile (0.24 g, 1 mmol), methylglyoxaldimethylacetal (0.12 mL, 1 mmol) and powdered KOH (60 mg, 1 mmol) in dry DMF (15 mL) was stirred at room temperature for 24 h and poured onto crushed ice with vigorous stirring, then neutralized with 10% HCl. The separated solid was filtered, washed with water, dried and purified by Si gel column chromatography, using hexane–chloroform (7:3) as eluent, mp 108 °C NMR (200 MHz, $CDCl_3$) δ 2.62 (s, 3H, SCH_3), 3.47 (s, 6H, OCH_3), 5.61 (s, 1H, CH), 7.45–7.48 (m, 4H, ArH), 7.61 (d, $J = 8.5$, 2H, ArH) 7.68 (s, 1H, ArH); IR (KBr) 2218 cm^{-1} (CN); MS m/z 300 (M^++1). Compound **3b**: oil, δ 1.26 (s, 2H, CH_2), 1.78–1.83 (m, 4H, CH_2), 3.18–3.23 (m, 4H, NCH_2), 3.46 (s, 6H, OCH_3), 5.61 (s, 1H, CH), 7.18 (s, 1H, ArH), 7.42–7.47 (m, 4H, ArH), 7.59 (d, $J = 6.28$, 2H, ArH); IR (KBr) 2216 cm^{-1} (CN); MS m/z 337 (M^++1). Compound **3c**: oil; δ 2.63 (s, 3H, SCH_3), 3.48 (s, 6H, OCH_3), 5.61 (s, 1H, CH), 7.17–7.27 (m, 2H, ArH), 7.41 (s, 1H, ArH), 7.54–7.63 (m, 3H, ArH); IR (KBr) 2219 cm^{-1} (CN); MS m/z 318 (M^++1). Compound **3d**: mp 92 °C; δ 1.98–2.05 (m, 4H, CH_2), 3.46 (s, 6H, OCH_3), 3.64–3.70 (m, 4H, NCH_2), 5.59 (s, 1H, CH), 6.78 (s, 1H, ArH), 7.15 (s, 1H, ArH), 7.40 (d, $J = 8.66$, 2H, ArH), 7.52 (d, $J = 8.66$, 2H, ArH); IR (KBr) 2257 cm^{-1} (CN); MS m/z 357 (M^++1). Compound **3e**: mp 122 °C; δ 2.62 (s, 3H, SCH_3), 3.46 (s, 6H, OCH_3), 5.60 (s, 1H, CH), 7.41 (s, 1H, ArH), 7.46 (d, $J = 9.0$, 2H, ArH) 7.61 (d, $J = 9.0$, 2H, ArH), 7.63 (s, 1H, ArH), IR (KBr) 2210 cm^{-1} (CN); MS m/z 379 (M^++1). Compound **3f**: oil; δ 2.53 (s, 3H, SCH_3), 2.61 (s, 3H, SCH_3), 3.46 (s, 6H, OCH_3), 5.60 (s, 1H, CH), 7.33 (d, $J = 8.35$, 2H, ArH) 7.44 (d, $J = 1.36$, 1H, ArH) 7.53 (d, $J = 8.35$, 2H, ArH) 7.65 (d, $J = 1.36$, 1H, ArH); IR (KBr) 2220 cm^{-1} (CN); MS m/z 346 (M^++1). Compound **3g**: oil; δ 2.43 (s, 3H, CH_3), 2.63 (s, 3H, SCH_3), 3.48 (s, 6H, OCH_3), 5.62 (s, 1H, CH), 7.29 (d, $J = 8.1$, 2H, ArH) 7.46 (d, $J = 1.2$, 1H, ArH) 7.52 (d, $J = 8.1$, 2H, ArH) 7.68 (d, $J = 1.2$, 1H, ArH); IR (KBr) 2219 cm^{-1} (CN); MS m/z 314 (M^++1). Compound **3h**: oil; δ 2.56 (s, 3H, SCH_3), 3.48 (s, 6H, OCH_3), 5.66 (s, 1H, CH), 7.39–7.55 (m, 6H, ArH), 7.61 (d, $J = 1.15$, 1H, ArH) 7.92–7.94 (m, 2H, ArH); IR (KBr) 2215 cm^{-1} (CN); MS m/z 350 (M^++1). Compound **3i**: oil; δ 2.55 (s, 3H, SCH_3), 3.35 (s, 6H, OCH_3), 3.96 (s, 3H, OCH_3), 5.66 (s, 1H, CH), 7.49–7.94 (m, 8H, ArH), 8.05 (s, 1H, ArH); IR (KBr) 2218 cm^{-1} (CN); MS m/z 383 (M^++1). Compound **3j**: oil; δ 1.50–1.56 (m, 2H, CH_2), 1.78–1.83 (m, 4H, CH_2), 3.17–3.23 (m, 4H, CH_2), 3.47 (s, 6H, OCH_3), 5.65 (s, 1H, CH), 7.11 (s, 1H, ArH), 7.12–7.90 (m, 8H, ArH); IR (KBr) 2213 cm^{-1} (CN); MS m/z 387 (M^++1). Compound **3k**: mp 78 °C; δ 2.61 (s, 3H, SCH_3), 3.45 (s, 6H, OCH_3), 5.57 (s, 1H, CH), 7.07–7.12 (m, 1H, ArH), 7.40 (d, $J = 5.1$, 1H, ArH) 7.45 (s, 2H, ArH), 7.68 (s, 1H, ArH); IR (KBr) 2210 cm^{-1} (CN); MS m/z 306 (M^++1).

Typical procedure A for Compound **4a**: A solution of **3a** (0.1 g, 0.33 mmol) in chloroform (10 mL) was stirred with Amberlyst 15 (30 mg) for 1 h. During this period complete conversion of the acetal to the corresponding aldehyde was observed. The catalyst was removed by filtration and evaporation of the solvent led to the desired compound in 95% yield.

Typical procedure B for Compound **4a**: A solution of **3a** (0.1 g) in 4% ethanolic-HCl (15 mL) was refluxed for 1 h. After evaporation of the solvent water (50 mL) was added. Extraction with chloroform followed by evaporation and purification on Si gel (chloroform–hexane (2:3) as eluent) gave **4a** in 60% yield, mp 108 °C; δ 2.67 (s, 3H, SCH_3), 7.48–7.55 (m, 3H, ArH), 7.60–7.65 (m, 2H, ArH), 7.72 (s, 1H, ArH), 7.96 (s, 1H, ArH), 10.39 (s, 1H, CHO); IR (KBr) 1704 cm^{-1} (CO), 2215 (CN); MS m/z 254 (M^++1). Compound **4b**: mp 110 °C; δ 1.57–1.62 (m, 2H, CH_2), 1.71–1.82 (m, 4H, CH_2), 3.18–3.26 (m, 4H, NCH_2), 7.36–7.55 (m, 6H, ArH), 7.69 (s, 1H, ArH), 10.31 (s, 1H, CHO); IR (KBr) 1704 cm^{-1} (CO), 2215 (CN); MS m/z 291 (M^++1). Compound **4c**: mp 128 °C; δ 2.60 (s, 3H, SCH_3), 7.10–7.19 (m, 3H, ArH), 7.50–7.59 (m, 2H, ArH), 7.85 (s, 1H, ArH), 10.33 (s, 1H, CHO); IR (KBr) 1703 cm^{-1} (CO), 2217 (CN); MS m/z 272 (M^++1). Compound **4d**: mp 136 °C; δ 2.03–2.12 (m, 4H, CH_2), 3.70–3.76 (m, 4H, NCH_2), 7.04 (s, 1H, ArH), 7.41–7.46 (m, 3H, ArH), 7.50–7.54 (m, 2H, ArH), 10.39 (s, 1H, CHO); IR (KBr) 1690 cm^{-1} (CO), 2197 (CN); MS m/z 311 (M^++1). Compound **4e**: mp 183 °C; δ 2.67 (s, 3H, SCH_3), 7.47–7.52 (m, 2H, ArH), 7.63–7.67 (m, 3H, ArH), 7.93 (s, 1H, ArH), 10.39 (s, 1H, CHO); IR (KBr) 1699 cm^{-1} (CO), 2219 (CN); MS m/z 333 (M^++1). Compound **4f**: oil; δ 2.54 (s, 3H, SCH_3), 2.67 (s, 3H, SCH_3), 7.35 (d, $J = 8.50$, 2H, ArH), 7.55 (d, $J = 8.50$, 2H, ArH), 7.69 (s, 1H, ArH), 7.95 (s, 1H, ArH), 10.38 (s, 1H, CHO); IR (KBr) 1705 cm^{-1} (CO), 2219 (CN); MS m/z 300 (M^++1). Compound **4g**: mp 126 °C; 2.45 (s, 3H, CH_3), 2.67 (s, 3H, SCH_3), 7.32 (d, $J = 7.6$, 2H, ArH), 7.53 (d, $J = 7.6$, 2H, ArH), 7.71 (s, 1H, ArH), 7.96 (s, 1H, ArH), 10.39 (s, 1H, CHO); IR (KBr) 1699 cm^{-1} (CO), 2212 (CN); MS m/z 268 (M^++1). Compound **4h**: oil; δ 2.61 (s, 3H, SCH_3), 7.42–7.98 (m, 9H, ArH) 10.42 (s, 1H, CHO); IR (KBr) 1702 cm^{-1} (CO), 2216 (CN); MS m/z 304 (M^++1). Compound **4j**: oil; δ 1.66 (s, 2H, CH_2), 1.78–1.89 (m, 4H, CH_2), 3.25–3.30 (m, 4H, NCH_2), 7.38 (s, 1H, ArH), 7.43 (s, 1H, ArH), 7.47–7.78 (m, 5H, ArH), 7.93 (d, $J = 7.42$, 2H, ArH), 10.41 (s, 1H, CHO) ; IR (KBr) 1704 cm^{-1} (CO), 2215 (CN); MS m/z 341 (M^++1). Compound **4k**: mp 128 °C; δ 2.67 (s, 3H, SCH_3), 7.14–7.19 (m, 1H, ArH), 7.46–7.52 (m, 2H, ArH), 7.70 (d, $J = 1.66$, 1H, ArH), 7.97 (d, $J = 1.66$, 1H, ArH), 10.36 (s, 1H, CHO); IR (KBr) 1703 cm^{-1} (CO), 2218 (CN); MS m/z 260 (M^++1).