Unmodified Nano-Powder Magnetite or Iron(III) Oxide Catalyze the Easy and Fast Synthesis of 4-Substituted-4*H*-Pyrans

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Dedicated to Prof. Dr. Alfredo Ricci on the occasion of his retirement

Abstract: Inexpensive and commercially available nano-power magnetite or iron(III) oxide can be used as catalyst in a new, straightforward, and fast protocol for the construction of 4-substituted-4*H*-pyrans. The reaction implies a tandem process, involving an aldol condensation, a Michael-type addition, and a dehydrating annulation.

Key words: annulation, heterocycles, heterogeneous catalysis, iron, pyrans

Pyrans and their benzo derivatives occupy an important area in natural chemistry, especially in plant life. The significant pharmacological and ecological activity shown by these systems has stimulated a great synthetic effort.¹ However, the preparation of the parent 4*H*-pyrans has been less developed, probably due to the presence of the dienol ether functionality and to the absence of aromatic character, which makes these types of compounds less stable. Beside these inconveniences, and since some of these architectures have important biological activities, including anticoagulant,² antioxidant,³ and as IK_{Ca} chanel blocker,⁴ several ways to build these compounds have been introduced.⁵

Among the different synthetic strategies used, the simple cascade process involving an aldol condensation, a Michael-type addition, and a final annulation dehydration has been scarcely used. For instance, the initial conditions to perform this task involved stoichiometric amounts of ZnCl₂, excess of acetic acid as dehydrating agent, and acetic anhydride as solvent during several weeks at room temperature rendering the 4-substituted-4*H*-pyyrans in 30-50% yields.⁶ A further improvement implied the use of ultrasound at 50 °C in acetic anhydride, which reduced the reaction time to several days and increased the yield up to 75%, avoiding the use of both the catalyst and the dehydrating agent.⁷ However, both protocols involve very harsh reaction conditions.⁸

In our ongoing project on the use of magnetite^{9,10} and metal-impregnated magnetite,¹¹ we realized that iron oxides could be an excellent catalyst for the aforementioned process avoiding these previous drawbacks.

SYNLETT 2011, No. 14, pp 2017–2020 Advanced online publication: 10.08.2011 DOI: 10.1055/s-0030-1261162; Art ID: S04011ST © Georg Thieme Verlag Stuttgart · New York Thus, we report here a simple, mild, and fast protocol to perform this tandem process using unmodified nanopower magnetite or iron(III) oxide as catalysts.

In order to optimize the reaction conditions, we studied the reaction between methyl 3-oxobutanoate (1a) and 4-bromobenzaldehyde (2a) to give the corresponding compound 4a,¹² as depicted in Table 1.

The uncatalyzed reaction using an excess of acetyl chloride (300 mol%) only produced a small amount of the aldol condensation product 3a, with the expected pyran being not detected. The reaction performed using only nanopower magnetite also failed, recovering both reagents unmodified and pointing out the need of both agents to obtain the expected product. So, when the reaction was repeated in the presence of magnetite and acetyl chloride (600 mol%), the expected pyran 4a was obtained after one day, together with the byproduct 3a (compare entries 1-3 in Table 1). Then, we studied the influence of other parameters such as the amount of acetyl chloride, with the presence of two equivalents being optimal (Table 1, entry 4). The decrease of the amount of catalyst produced a decrease in the yield (Table 1, entries 5 and 6). The use of other solvents such as dioxane, diethyl ether or hexane reduced significantly the yield (Table 1, entries 7–9). The reaction performed under basic conditions failed (Table 1, entry 10), and other acid chloride derivatives gave in all cases worse results than those obtained with acetyl chloride (Table 1, compare entries 4 and 11–16), even in the case of acetic anhydride (Table 1, entry 17). Then, we repeated the reaction with commercial micropowder magnetite, the product being obtained with lower yield (Table 1, entry 18). Then, we faced the problem which iron center could be responsible for the reaction, performing the reaction with iron oxide. In the case of iron(II), the reaction only produced the aldol condensation product **3a**, with the expected pyran being undetected (Table 1, entry 19). However, in the case of nanopowder iron(III) oxide, we obtained practically the same result as using magnetite (Table 1, compare entries 4 and 20). Although in the magnetite the amount of iron(III) centers is half the number of those in pure iron(III) oxide, the reduction of the amount of catalyst decreased the yield of desired product 4a, even more than for magnetite (Table 1, compare entries 5, 6, 21, and 22). Then, we thought that the different iron oxides could only play a marginal role as catalyst, being only the source of the corresponding iron chloride. To prove

this hypothesis, we repeated the reaction using iron(III) and iron(II) chloride, and the yields of compound **4a** were significantly lower than using the related oxides, with the initial formed aldol condensation derivative **3a** being the main isolated product in both cases (Table 1, entries 23 and 24). Finally, it should be pointed out that both iron oxides could be easily removed from the reaction media just by filtration.

After finding that both, magnetite or iron(III) oxide, could be successfully used in the tandem formation of 4H-pyrans, we tested different impregnated metallic oxides on magnetite with the hope that these oxides could improve the obtained results (Table 2). The reactions performed under similar reaction conditions to those presented in entry 4 of Table 1 with different catalysts gave always worse results, independently of the metallic oxide used (Table 2, entries 1–7). Only the palladium derivatives gave similar results.

Once we realized that both magnetite and iron(III) oxide were excellent catalysts for this transformation, we studied the scope of the reaction (Table 3).

The isolated yields of pyrans 4 were similar independently of the aromatic aldehyde used, with electron-withdrawing groups (Table 3, entries 1 and 2), unsubstituted rings (Table 3, entry 3), or electron-donating groups (Table 3, entries 4 and 5) being well tolerated. It should be pointed out that in the case of 4-hydroxybenzaldehyde, the corresponding hydroxy pyran 4e was isolated, not detecting the related acylated pyran. The reaction with a sterically more congested 2-naphthylcarbaldehyde gave a lower yield (Table 3, entry 6). The results obtained using aliphatic aldehydes were good for cyclic and acyclic derivatives (Table 3, entries 7 and 8). The change of the ester moiety in the 1,3-dicarbonyl reagent did not have any influence on the achieved results (Table 3, compare entries 1, 4, 9, and 10). Instead of β -keto esters, other 1,3-dicarbonyl compounds could be used as pentane-2,4-dione, obtaining the corresponding pyran 4k with similar results (Table 3, entry 11). The substitution at the 2,6-positions of the pyran could be changed only by using the appropriated substituted 1,3-dicarbonyl compounds. Thus, the reaction of methyl 3-oxopentanoate with 4-bromobenzaldehyde (2a) gave the expected compound 41 with the same practical results, independently of the catalyst used (Table 3, entry 12).

Finally, we applied the same protocol to the dialdehyde **6** (Scheme 1), just increasing the corresponding amount of carbonyl compounds and acid chloride, yielding the expected product **7** with good yield, with similar results being obtained by using iron(III) oxide (71%).

Although the possible mechanism is still unknown, it should be pointed out that the formation of a catalytic species having an Fe(III)–Cl bond should play an important role as a Lewis acid, with the centers of iron(III) being the only avail to catalyze the final Michael addition (see above).

Table 1 Optimization of the Reaction Conditions^a



Entry	Catalyst (mol%)	Dehydrating agent	Solvent	Time (h)	Yield of 3a/4a (%)
1	_	MeCOCl ^b	PhMe	72	18/0
2	Fe ₃ O ₄ (65)	-	PhMe	72	0/0
3	Fe ₃ O ₄ (65)	MeCOCl ^c	PhMe	24	22/73
4	Fe ₃ O ₄ (65)	MeCOCl	PhMe	3	3/96
5	Fe ₃ O ₄ (32)	MeCOCl	PhMe	3	10/85
6	$Fe_{3}O_{4}(7)$	MeCOCl	PhMe	3	26/45
7	Fe ₃ O ₄ (65)	MeCOCl	1,4-dioxane	3	30/28
8	Fe ₃ O ₄ (65)	MeCOCl	Et ₂ O	3	56/9
9	Fe ₃ O ₄ (65)	MeCOCl	hexane	3	7/64
10	Fe ₃ O ₄ (65)	NaOH	PhMe	72	0/0
11	Fe ₃ O ₄ (65)	PhCOCl	PhMe	72	38/14
12	Fe ₃ O ₄ (65)	ClCH ₂ COCl	PhMe	72	11/2
13	Fe ₃ O ₄ (65)	HCCl ₂ COCl	PhMe	72	5/0
14	Fe ₃ O ₄ (65)	HCBr ₂ COCl	PhMe	72	0/0
15	Fe ₃ O ₄ (65)	TsCl	PhMe	72	0/0
16	Fe ₃ O ₄ (65)	TMSCl	PhMe	72	8/15
17	Fe ₃ O ₄ (65)	(MeCO) ₂ O	PhMe	72	0/0
18 ^d	Fe ₃ O ₄ (65)	MeCOCl	PhMe	3	27/57
19	FeO (65)	MeCOCl	PhMe	3	63/0
20	Fe ₂ O ₃ (65)	MeCOCl	PhMe	3	5/94
21	$Fe_2O_3(32)$	MeCOCl	PhMe	3	24/55
22	$Fe_2O_3(7)$	MeCOCl	PhMe	3	39/30
23	FeCl ₃ (65)	MeCOCl	PhMe	3	38/13
24	FeCl ₂ (65)	MeCOCl	PhMe	3	39/25

^a Reaction carried out using compound **1a** (2.5 mmol), **2a** (1 mmol), and MeCOCl (2 mmol) in 3 mL of solvent, unless otherwise stated.

^b Reaction performed using 300 mol%.

^c Reaction performed using 600 mol%. ^d Reaction performed with micromagnetite.



^a Reaction carried out using compound **1a** (2.5 mmol) and **2a** (1 mmol) in 3 mL of toluene during 3 h.

In conclusion, we have demonstrated that both magnetite and iron(III) oxide are good catalysts for the pyran formation tandem reaction. The process could be performed with a broad range of substrates, keeping the high level of the results, avoiding the use of high temperature, and reducing the reaction time from weeks to hours.



Scheme 1 Double tandem process

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Table 3 Synthesis of 4-Substituted-4H-Pyrans^a

) +)		Fe ₃ O ₄ or Fe ₂ O ₃ (65 mol%) MeCOCI (200 mol ⁴ PhMe, 25 °C, 3	→ Y´ %), h		O ↓ Y
1		2			4	
Entry	\mathbb{R}^1	Y	\mathbb{R}^2	Pyran	Yield (%)	Mp (°C) ^b
1	Me	OMe	$4\text{-}BrC_6H_4$	4 a	96 (94)	98
2	Me	OMe	$4-NCC_6H_4$	4 b	79	92
3	Me	OMe	Ph	$4c^4$	85 (82)	61
4	Me	OMe	4-MeOC ₆ H ₄	4d ¹³	83	112
5	Me	OMe	$4-HOC_6H_4$	4e	68	119
6	Me	OMe	2-naphthyl	4f	57°	125
7	Me	OMe	(CH ₂) ₅ CH	4 g	80° (79°)	65
8	Me	OMe	<i>i</i> -Pr	4h	72 (67)	46
9	Me	OEt	4-BrC ₆ H ₄	4i ⁷	95	75 ^d
10	Me	OEt	4-MeOC ₆ H ₄	$4j^7$	63	84 ^e
11	Me	Me	4-MeOC ₆ H ₄	4k	75° (64)	83
12	Et	OMe	$4-BrC_6H_4$	41	91 (92)	68

^a Reaction carried out using compound 1 (2.5 mmol), 2 (1 mmol), in 3 mL of toluene during 3 h, unless otherwise stated. Yields obtained by Fe_2O_3 catalysis appeared in parenthesis.

^b Recrystallized from mixtures of EtOAc and hexane.

^c Reaction performed during 5 h.

^d Mp 81 °C (ref. 7).

^e Mp 83-85 °C (ref. 7).

References and Notes

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- (12) Representative Procedure for the Synthesis of Dimethyl 4-(4-Bromophenyl)-2,6-dimethyl-4H-pyran-3,5-dicarboxylate (4a)
 To a stirred solution of 4-bromobenzaldehyde (2a, 1 mmol) in toluene (3 mL) were added Fe₃O₄ (50 mg, 65 mol%),

methyl 3-oxobutanoate (1a, 2.5 mmol), and AcCl (0.14 mL,

2 mmol). The resulting mixture was stirred at 25 °C during 3 h. The mixture was quenched with H2O (5 mL) and extracted with EtOAc $(3 \times 5 \text{ mL})$. The organic phases were dried over MgSO₄, followed by evaporation under reduced pressure to remove the solvent. The product was purified by chromatography on silica gel (hexane-EtOAc) to give the titled product; mp 96–100 °C(hexane). $R_f = 0.5$ (hexane–EtOAc = 4:1). IR (KBr) : v = 1721, 1671, 1629, 1584, 1296 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): $\delta = 2.36$ (6 H, d, J = 0.6 Hz, 2 × CCH₃), 3.64 (6 H, s, 2 × CO₂CH₃), 4.72 (1 H, s, CH), 7.10 (2 H, d, J = 8.5 Hz, 2 × BrCCHCH), 7.36 (2 H, d, J = 8.5 Hz, 2 × BrCCH). ¹³C NMR (75 MHz, CDCl₃): $\delta =$ 18.7 (2 C), 37.8, 51.4 (2 C), 107.7 (2 C), 120.4, 129.9 (2 C), 131.2 (2 C), 144.3, 158.7 (2 C), 166.9 (2 C). CG-MS: m/z $(\%) = 382 (11) [M^+ + 2], 380 (11) [M^+], 367 (14), 365 (13),$ 323 (14), 321 (14), 226 (11), 225 (100), 193 (11). HRMS: *m/z* calcd for C₁₇H₁₇BrO₅: 382.0259; found: 380.0256.

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