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Zirconium(IV) Compounds As Efficient Catalysts for Synthesis of α-Aminophosphonates

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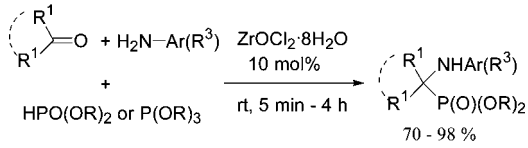
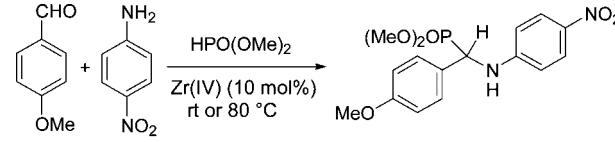


Zirconium(IV) compounds are reported as excellent catalysts for a three-component one-pot reaction of an amine, an aldehyde or a ketone, and a di/trialkyl/aryl phosphite to form α-aminophosphonates under solvent-free conditions at rt. Among the various zirconium compounds, $ZrOCl_2 \cdot 8H_2O$ and $ZrO(ClO_4)_2 \cdot 6H_2O$ were most effective. The reactions were faster with dialkyl/diaryl phosphites than with trialkyl/triaryl phosphites. No *O*−Me cleavage occurs with aryl methyl ether and methyl ester groups. α,β-Unsaturated carbonyl moiety does not undergo conjugate addition with the phorphorous moiety.

The versatile biological activities[1] of α-aminophosphonates have rendered the α-aminophosphonate moiety the status of a novel pharmacophore in the context of drug design. Thus, efforts are made toward the development of new methods for their synthesis.[2] There has been an increasing influence of green chemistry on medicinal chemistry and research chemistry-based organization.[3] This requires maintaining greenness in synthetic pathways/processes by prevention of waste generation, avoiding the use of auxiliary substances (e.g., solvents, additional reagents) and minimizing the energy requirement.[4] These press the need of a convenient and high-yielding synthetic method for the timely supply of the designed new chemical entities for biological evaluation.[5]

Recently anhydrous $Mg(ClO_4)_2$ has been reported as an effective catalyst for the synthesis of α-aminophosphonates.[6] However, its catalytic activity decreases on exposure to air/moisture due to the formation of the hydrate. The high charge-to-size[7] value of Zr^{4+} offers Zr(IV) compounds strong electrophilic activation properties. Due to their abundance in the earth's crust,[8] Zr(IV) compounds are easily available and less costly. Zirconium(IV) compounds display no redox character but can attain a covalency maximum up to 8 and are of low toxicity.[9]

SCHEME 1. Reaction of 1a, 2a and Dimethyl Phosphite in the Presence of Zr(IV) Compounds.



1a **2a**

In search for an effective catalyst and the best operative experimental conditions, the reaction of 4-methoxybenzaldehyde (**1a**) as a representative less electrophilic aldehyde, 4-nitroaniline (**2a**) as an electron-deficient amine and dimethyl phosphite (Scheme 1) was considered as the model reaction, and various Zr(IV) compounds were tested as catalysts (Table 1).

The best results were obtained in using 10 mol % of $ZrOCl_2 \cdot 8H_2O$ or $ZrO(ClO_4)_2 \cdot 6H_2O$ at rt for 30 min (yields 92 and 98%) and at 80 °C for 5 min (yields 92 and 95%) under neat conditions. The use of solvents such as DCM, MeCN and THF required longer times (2−8 h) to afford comparable yields. The necessity to use the catalyst was realized by the observations that poor yields (30−50%) were obtained when the reactions

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(2) Recent examples: (a) Bhattacharya, A. K.; Kaur, T. *Synlett* **2007**, 745. (b) Wu, J.; Sun, W.; Sun, X.; Xia, H.-G. *Green Chem.* **2006**, *8*, 365. (c) Kaïm, L. E.; Grimaud, L.; Hadrot, S. *Tetrahedron Lett.* **2006**, *47*, 3945. (d) Mu, X.-J.; Lei, M.-Y.; Zou, J.-P.; Zhang, W. *Tetrahedron Lett.* **2006**, *47*, 1125. (e) Kabachink, M. M.; Zobnina, E. V.; Beletskaya, I. P. *Synlett* **2005**, 1393. (f) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2989. (g) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 1209. (h) Zhan, Z.-P.; Yang, R.-F.; Li, J.-P. *Chem. Lett.* **2005**, *34*, 1042. (i) Ghosh, R.; Maiti, S.; Chakraborty, A.; Maiti, D. K. *J. Mol. Catal. A* **2004**, *210*, 53. (j) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692. (k) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (l) Azizi, N.; Rajabi, F.; Saidi, M. R. *Tetrahedron Lett.* **2004**, *45*, 9233. (m) Azizi, N.; Saidi, M. R. *Tetrahedron* **2003**, *59*, 5329. (n) Matveeva, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G.; Zefirov, N. S. *Synlett* **2003**, 2321. (o) For a review, see: Kukhar, V. P.; Soloshonok, V. A.; Solodenko, V. A. *Phosphorus Sulfur Silicon Relat. Elem.* **1994**, *92*, 239.

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TABLE 1. Reaction of 1a, 2a and Dimethyl Phosphite in the Presence of Various Zr(IV) Compounds.[a]

entry	catalyst	solv	temp (°C)	time (h)	yield (%)[b]
1	$ZrCl_4$	neat	rt	1	80
2	$ZrCl_4$	neat	80	10 min	85
3	$ZrCl_4$	DCM	rt	8	60
4	$ZrCl_4$	MeCN	rt	8	60
5	$ZrBr_4$	neat	rt	1	80
6	ZrF_4	neat	rt	1	80
7	$Zr(OH)_4$	neat	rt	1	50
8	$ZrO(NO_3)_2 \cdot xH_2O$	neat	rt	1	50
9	$Zr(OPr^i)_4 \cdot {}^i PrOH$	neat	rt	1	60
10	$ZrSiO_4$	neat	rt	1	50
11	$Zr(acac)_4$	neat	rt	1	40
12	ZrO_2	neat	rt	1	30
13	ZrC	neat	rt	1	30
14	$Zr(OH)_2(OAc)_2$	neat	rt	1	40
15	$ZrCp_2Cl_2$	neat	rt	1	50
16	$Zr(C_5H_4F_3O_2)_4$	neat	rt	1	50
17	$ZrSi_2$	neat	rt	1	30
18	ZrB_2	neat	rt	1	30
19	$Zr(SO_4)_2 \cdot xH_2O$	neat	rt	1	40
20	$2BiO_3 \cdot 3ZrO_2$	neat	rt	1	50
21	$MgZrO_3$	neat	rt	1	50
22	$ZrOCl_2 \cdot 8H_2O$	DCM	rt	2	95
23	$ZrOCl_2 \cdot 8H_2O$	MeCN	rt	6	80
24	$ZrOCl_2 \cdot 8H_2O$	EtOH	rt	6	85
25	$ZrOCl_2 \cdot 8H_2O$	hexane	rt	6	60
26	$ZrOCl_2 \cdot 8H_2O$	THF	rt	8	80
27	$ZrOCl_2 \cdot 8H_2O$	neat	rt	0.5	92
28	$ZrOCl_2 \cdot 8H_2O$	neat	80	5 min	92
29	$ZrO(ClO_4)_2 \cdot 8H_2O$	neat	rt	0.5	98
30	$ZrO(ClO_4)_2 \cdot 8H_2O$	neat	80	5 min	95
31	$ZrO(ClO_4)_2 \cdot 8H_2O$	DCM	rt	2	95
32	none	neat	80	24	50
33	none	neat	rt	24	30
34	none	DCM	rt	24	30
35	none	DCE	reflux	24	50

[a] **1a** (2.5 mmol) was treated with **2a** (2.5 mmol) and dimethyl phosphite (3 mmol) in the presence of the catalyst (10 mol %) except for entries 32−35 where no catalyst was used under solvent-free conditions (except for entries 3, 4, 22−26, 31, 34 and 35). [b] Yield of the α-aminophosphonate obtained after purification.

were carried out in the absence of any catalyst either at rt or at 80 °C under neat conditions or in DCM/DCE for 24 h.

The reaction of **1a**, aniline (**2b**), and various dialkyl/trialkyl phosphites and diaryl/triaryl phosphites were next carried out in the presence of $ZrOCl_2 \cdot 8H_2O$ to determine the influence of the phosphite (Table 2). The reactions were faster with dialkyl/diaryl phosphites than with the corresponding trialkyl/triaryl phosphites. In case of dialkyl/trialkyl phosphites, the increase in the alkyl chain or branching at the alkyl chain decreased the reaction rate (compare entries 1−3 and 5 and entries 6−10, Table 2).

To establish generality, various aldehydes/ketones, amines and dimethyl/diethyl phosphites were subjected to a one-pot reaction (Table 3). Although $ZrOCl_2 \cdot 8H_2O$ and $ZrO(ClO_4)_2 \cdot 6H_2O$ were equally effective, we preferred to use $ZrOCl_2 \cdot 8H_2O$, as it is cheap and less hygroscopic.

Excellent results were obtained during the reaction of aryl/heteroaryl/aryl alkyl aldehydes/ketones with aryl/heteroaryl/alryl alkyl amines and dimethyl/diethyl phosphites. The reaction was compatible with various functional groups such as Cl, OMe, NO_2, OH, NMe_2, CN, and CO_2Me that do not interfere by competitive complex formation with the catalyst. Excellent

TABLE 2. Reaction of 1a, 2b and Various Phosphites in the Presence of $ZrOCl_2 \cdot 8H_2O$.[a]

entry	phosphites	time (min)	yield (%)[b]
1	$HP(O)(OMe)_2$	10>	95[c]
2	$HP(O)(OEt)_2$	10	90
3	$HP(O)(OBu^n)_2$	30	90
4	$HP(O)(OPh)_2$	5	90
5	$HP(O)(OBz)_2$	30	80
6	$P(OMe)_3$	10	90
7	$P(OEt)_3$	15	90
8	$P(OPr^i)_3$	90	70
9	$P(OBu^n)_3$	60	90
10	$P(OPh)_3$	120	70

[a] **1a** (2.5 mmol) was treated with **2b** (2.5 mmol) and the phosphite (3 mmol) in the presence of $ZrOCl_2 \cdot 8H_2O$ (2.5 mol %). [b] Yield of the α-aminophosphonate obtained after purification. [c] The α-aminophosphonate was obtained in 85% yield in carrying out the reaction for 5 min.

chemoselectivity was observed for substrates containing a halogen atom (entries 3, 18, and 19, Table 3) and having a double bond conjugated to a carbonyl group (entries 32 and 33, Table 3) that did not experience any competitive aromatic nucleophilic substitution of the halogen atom and conjugate addition to the α,β-unsaturated carbonyl group, respectively. No competitive nucleophilic cleavage of the *O*-Me group was observed for substrates having an aryl methyl ether (entries 6−14, 16, 17, 22, 23, and 44−53, Table 3) or methyl ester (entry 16, Table 3) groups although phosphites possess good nucleophilic properties.[10] The reaction with dimethylacetal of aminoacetaldehyde (entry 50, Table 3) further exemplified the case of chemoselectivity and mildness of the reaction, as no competitive nucleophilic substitution of the *O*-Me group or cleavage of the acetal moiety or condensation of the acetal moiety with the NH_2 group took place. Excellent yields were obtained for reaction with sterically hindered aromatic (entries 8 and 10−13, Table 3) and aliphatic (entry 51, Table 3) amines and electron-deficient amines (entries 7–16, 18–21, 38, 42, 52 and 53, Table 3). However, the reactions needed to be carried out for longer periods for electron-deficient and sterically hindered amines. The longer time required for 1-naphthaldehyde (entries 24 and 25, Table 3) compared to those for 2-naphthaldehyde (entries 26 and 27, Table 3) was due to the steric hindrance caused by the peri-hydrogen atom in the former.

The formation of α-aminophosphonate is reported to follow two distinct pathways:[11] (i) imine formation followed by nucleophilic attack by the phosphite[12] and (ii) nucleophilic displacement of the hydroxyl group of the initially formed α-hydroxyphosphonate.[13] Thus, in separate experiments we treated (a) 4-methoxybenzaldehyde (**1a**) with 4-nitroaniline (**2a**) (b) **1a** with dimethyl phosphite in the presence of $ZrOCl_2 \cdot 8H_2O$ (2.5 mol%) at 80 °C for 6 h. However, no imine formation was observed (IR, NMR, MS) in the former, and no significant amount of the corresponding α-hydroxyphosphonate (IR, NMR, MS) was formed in the second case. Thus, in the absence of intermediate formation of the imine/α-hydroxyphosphonate, this probably represents a three-component reaction (3CR) in which

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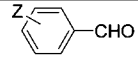
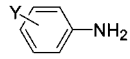
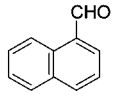
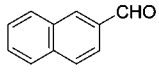
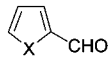
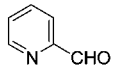
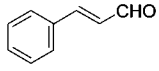
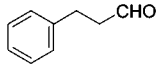
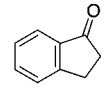
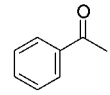
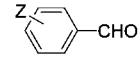
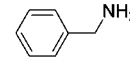
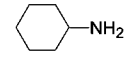
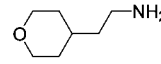
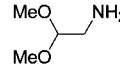
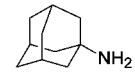
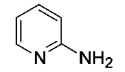
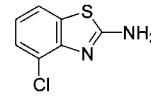
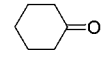
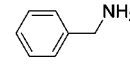
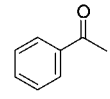
TABLE 3. Synthesis of α-Aminophosphonate by the Reaction of Various Aldehydes/Ketones, Amines and Dimethyl/Diethyl Phosphite in the Presence of $ZrOCl_2 \cdot 8H_2O$.[a]

entry	aldehyde/ ketone	amine	time (min)	yield (%)[b,c]
				
1	Z = H	Y = H	5	96
2	Z = H	Y = H	5	95[d]
3	Z = 4-Cl	Y = H	10	90
4	Z = 4-CN	Y = H	10	90
5	Z = 4-NMe_2	Y = H	10	85
6	Z = 3,5-di-OMe, 4-OH	Y = H	10	90
7	Z = 4-OMe	Y = 4-NO_2	30	92
8	Z = 4-OMe	Y = 2-NO_2	30	90
9	Z = 4-OMe	Y = 3-NO_2	10	90
10	Z = 4-OMe	Y = 2,4-di-NO_2	120	85
11	Z = 2,4-di-OMe	Y = 2,4-di-NO_2	180	80
12	Z = 2,4,6-tri-OMe	Y = 2,4-di-NO_2	240	80
13	Z = 3,4,5-tri-OMe	Y = 2,4-di-NO_2	220	80
14	Z = 4-OMe	Y = 4-CN	20	90
15	Z = H	Y = 4-COMe	10	90
16	Z = 4-OMe	Y = 4-CO_2Me	30	90
17	Z = 4-OMe	Y = 4-OH	20	90
18	Z = 4-Cl	Y = 4-NO_2	10	85
19	Z = 4-Cl	Y = 3-NO_2	10	85
20	Z = 4-NO_2	Y = 4-NO_2	20	86
21	Z = 4-NO_2	Y = 4-NO_2	15	83[d]
22	Z = 2,4,6-tri-OMe	Y = H	15	85
23	Z = 3,4,5-tri-OMe	Y = H	20	85
				
24		Y = H	20	90
25		Y = H	20	80[d]
				
26		Y = H	10	92
27		Y = H	10	90[d]
				
28	X = O	Y = H	10	81
29	X = O	Y = H	10	78[d]
30	X = S	Y = H	10	81[d]
				
31		Y = H	15	82
				
32		Y = H	15	85
33		Y = H	15	75[d]
				
34		Y = H	20	75
				
35		Y = H	20	70
				

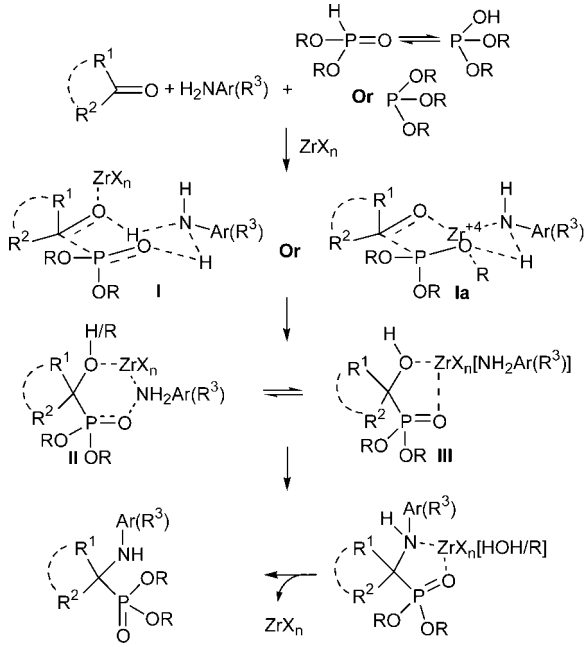
entry	aldehyde/ ketone	amine	time (min)	yield (%)[b,c]
36		Y = H	120	80
37		Y = H	120	70[d]
38		Y = 4-NO_2	180	75[e]
				
39		Y = H	240	75[e]
				
40		Y = H	240	80[e]
41		Y = H	240	80[d,e]
42		Y = 4-NO_2	360	75[e]
				
43	Z = H		10	92
44	Z = 4-OMe		10	90
				
45	Z = 4-OMe		20	96
				
46	Z = 4-OMe	X = CH_2	15	90
47	Z = 4-OMe	X = O	15	90
				
48	Z = 4-OMe		15	90
				
49	Z = 4-OMe		30	80
				
50	Z = 4-OMe		10	95
				
51	Z = 4-OMe		30	95
				
52	Z = 4-OMe		15	90
				
53	Z = 4-OMe		60	70[e]
				
54			120	90
55			120	91[d,e]
				
56			240	80[d,e]

[a] The aldehyde/ketone (2.5 mmol) was treated with the amine (2.5 mmol) and dimethylphosphite (3 mmol) (except for entries 2, 21, 25, 27, 29, 30, 33, 37, 41, 55 and 56) in the presence of $ZrOCl_2 \cdot 8H_2O$ (10 mol%) at rt (except for entries 38−42 and 53−56) under solvent-free conditions. [b] Yield of the purified α-aminophosphonate. [c] The product was characterized by IR, ^1H and ^{13}C NMR and MS. [d] The reaction was carried out using diethyl phosphite instead of dimethyl phosphite. [e] The reaction was carried out at 80 °C.

all the three reactants/components are simultaneously involved in the product formation (Scheme 2).

The ability of the OH group of dialkyl/diaryl phosphites to form a hydrogen bond makes the intermediate **I** more rigid compared to **Ia** from the trialkyl/triaryl phosphites. The faster reaction with $HOP(OPh)_2$ than that with the dialkyl phosphites is due to the more efficient hydrogen-bond formation, as the electron-withdrawing effect of the phenyl/phenoxy group makes the phosphorus atom electron deficient. On the other hand, as the OPh moiety is an inferior hydrogen-bond acceptor compared

SCHEME 2. Role of Zr(IV) Compounds.



to the OR group, the reaction is slower with $P(OPh)_3$, as in case of the trialkyl phosphites the formation of the hydrogen-bonded intermediate **Ia** is facilitated through the OR group.

In summary, commercially available $ZrOCl_2 \cdot 8H_2O$ and $ZrO(ClO_4)_2 \cdot 6H_2O$ are efficient catalysts for synthesis of α-aminophosphonates by a three-component (3CR) one-pot reaction. The advantages such as the (i) solvent-free reaction,[14] (ii) high yields, (iii) excellent chemoselectivity (iv) and use of easily available, cheap and safer catalysts.

Experimental Section

Typical Representative Procedure. Dimethyl [(4-methoxyphenyl)-(4-nitrophenylamino)methyl]phosphonate[6a]. (Table 3, entry 7): The mixture of 4-methoxybenzaldehyde **1a** (0.34 g, 2.5 mmol), 4-nitroaniline **2a** (0.345 g, 2.5 mmol), dimethyl phosphite (0.33 g, 3 mmol), and $ZrOCl_2 \cdot 8H_2O$ (81 mg, 0.25 mmol) in a 10 mL round-bottom flask was stirred magnetically under neat condition at rt (~35 °C) for 30 min (or at 80 °C for 5 min). After completion of the reaction (TLC), the organic mixture was extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were washed with water (5 mL), dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by flash chromatography using EtOAc-hexane (70:30) as the eluent to afford the desired α-aminophosphonate as yellow solid (0.84 g, 92%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.46 (d, 3 H, J = 11.55 Hz), 3.76 (d, 3 H, J = 10.78 Hz), 3.78 (s, 3 H), 4.77−4.84 (d, 1 H, $^1J_{P-H}$ = 24.67 Hz), 6.58 (d, 2 H, J = 9.18 Hz), 6.88 (2 H, d, J = 8.61 Hz), 7.36 (m, 2 H), 7.99 (d, 2 H, J = 9.15 Hz).^{13}C NMR ($CDCl_3$, 75 MHz): δ 53.4, 53.6, 54.2, 55.3, 55.5, 112.4, 114.5, 125.9, 128.8, 132.3, 139,151.7, 151.8, 159.8; MS m/z 366 $(M)^+$, 257 $[(M - P(O)(OMe)_2]^+$.

Acknowledgment. We thank OPCW, Hague, The Netherlands, for financial support.

Supporting Information Available: Spectral data of all compounds, scanned spectra of a few representative known and all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Garrett, R. L. In *Designing Safer Chemicals*; Garrett, R. L., De Vito, S. C., Eds.; American Chemical Society Symposium Series 640; American Chemical Society: Washington, D.C., 1996; Chapter 1.