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Lewis Acid-Mediated Michaelis–Arbuzov Reaction at Room Temperature: A Facile Preparation of Arylmethyl/Heteroarylmethyl Phosphonates

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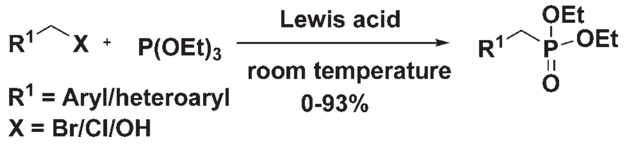
ABSTRACT



A facile preparation of arylmethyl and heteroarylmethyl phosphonate esters was achieved involving a Lewis acid mediated Michaelis–Arbuzov reaction at room temperature. Interaction of arylmethyl halides/alcohols with triethyl phosphite in the presence of Lewis acid at room temperature afforded phosphonate esters in good yields.

Organic phosphonates are a key functional group in biological chemistry as well as synthetic organic chemistry.[1] In particular, arylmethyl and heteroarylmethyl phosphonate esters have been widely utilized as prominent precursor for the synthesis of optical materials such as poly(phenylvinylenes),[2] thienylvinylenes,[3] trialkylamine tethered vinylenes,[4] as well as stilbene dendrimers[5] involving a Horner–Wadsworth–Emmons reaction[6] with aldehydes. The required organophosphonate esters have been traditionally obtained through a Michaelis–Arbuzov reaction.[7]

The Michaelis–Arbuzov reaction is initiated with an S_N2 reaction of nucleophilic trialkylphosphite with arylmethyl halides to give a phosphonium intermediate. The displaced halide anion upon a second S_N2 reaction with phosphonium intermediate led to the phosphonate ester along with an alkyl halide. Despite its acceptance, the Michaelis–Arbuzov reaction has two major drawbacks. First, the elevated temperature required for the activation of the reaction, limits the scope of the substrate suitable for the reaction. Second, the reaction generates one equiv of alkyl halide, which can react with the phosphite under reaction conditions to reduce yield and reaction efficiency. The Michaelis–Becker reaction[8] utilizing dialkylphosphite salt of alkali metals with alkyl halides somewhat

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[7] (a) Michaelis, A.; Kaehne, R. *Chem. Ber.* **1898**, *31*, 1048–1058. (b) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 315–370. (c) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.

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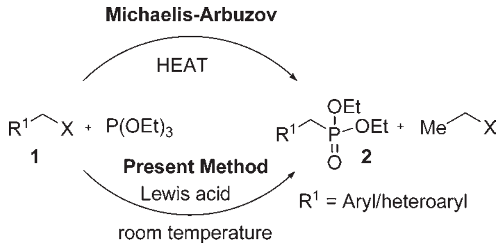
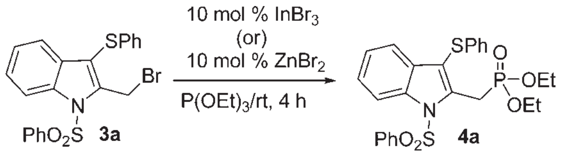
overcomes the above-mentioned problems. However, the reaction conditions are often not convenient requiring either the use of strong anhyd base,[9] or longer reaction time[10] and in some cases resulted in low yield of the phosphonates.[11] Salvatore and co-workers achieved a mild and efficient synthesis of phosphonates via interaction of dialkylphosphonates with alkyl halides in the presence of Cs_2CO_3 and TBAI in dry DMF at room temperature.[12]

Recently, an efficient preparation of benzyl phosphonates was achieved involving the $Pd(OAc)_2$-mediated cross-coupling reaction of benzyl halides with H-phosphonate diesters using Xantphos as a supporting ligand.[13] Peyrottes et al. achieved the synthesis of sugar and nucleoside phosphonate derivatives involving microwave-assisted Michaelis−Arbuzov reaction.[14] Marder and co-workers reported a convenient method for the synthesis of electron-rich benzyl phosphonates by treating the corresponding alcohols with triethyl phosphite in the presence of 1 equiv of I_2 at room temperature.[15] This method proved to be useful for highly electron-rich heteroaryl methyl alcohols. However, in the case of less electron-rich systems, the method requires high temperature. Pei and co-workers achieved the synthesis of alkyl phosphonate esters via interaction of heteroarylmethyl alcohols with triethyl phosphite and I_2 in the presence of DBU at elevated temperature.[16] Very recently, a room-temperature alternative to the Michaelis−Arbuzov reaction was realized through reductive dehydrogenation of acyl phosphonates.[17] Using this method, a one-pot sequence for the synthesis of alkyl phosphonates was developed from carboxylic acids. An efficient synthesis of α-aminophosphonates via interaction of *N*-benzyloxycarbonylamino sulfones with triethyl phosphite in the presence of a catalytic amount of $InCl_3$ in DCM at room temperature was achieved.[18] In continuation of our studies on Lewis acid mediated domino reactions,[19] we report herein the Lewis acid mediated Michaelis−Arbuzov reaction of benzylic bromides **1** with triethyl phosphite at room temperature (Scheme 1).

Scheme 1. Michaelis−Arbuzov Reaction



Scheme 2. Lewis Acid-Mediated Michaelis−Arbuzov Reaction



In our ongoing program on the synthesis of carbazole alkaloids, we required various types of *N*-phenylsulfonyl-2/3-indolylmethylphosphonates as starting materials. The accessibility of these phosphonate esters using the traditional method at elevated temperature was problematic due to the unstable nature of the bromomethylindoles. Our recent success with the Lewis acid mediated domino reaction of bromomethylindoles prompted us to explore a Lewis acid mediated Michaelis−Arbuzov reaction of the same. Accordingly, when the reaction of bromomethylindole **3a** was performed with triethyl phosphite in the presence of 10 mol % of $InBr_3$ at room temperature for 4 h followed by workup led to the isolation of known phoshponate ester **4a** in 80% yield (Scheme 2). Gratifyingly, the reaction could also be carried out at room temperature using less expensive $ZnBr_2$ as a catalyst in almost comparable yield. This unexpected Lewis acid-mediated Michaelis−Arbuzov reaction of the bromomethylindole **3a** at room temperature prompted us to study the reaction with other benzylic halides.

To our delight, the Lewis acid-mediated Michaelis−Arbuzov reaction of a wide variety of aryl as well as heteroarylmethyl bromides could be successfully performed at room temperature to afford the corresponding phosphonates in good yields (Table 1). The 2-indolylmethanols **3b** and **3d** also underwent a smooth Lewis acid mediated Michaelis−Arbuzov reaction at room temperature in the presence of 1.1 equiv of $ZnBr_2$ (entry 1). Comparatively, 2-chloromethylindole **3a′**/**3c′** produced the respective phosphonate ester in diminished yield than the 2-bromomethylindole **3a**/**3c** (entry 1).

With the exception of 3-chloromethylindole **3l′**, in all other cases the reaction was found to be successful even in the presence of electron-withdrawing functional groups (entries 1−3). The reaction of bromomethyl ketone **3o**

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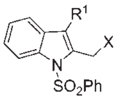
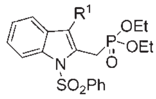
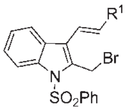
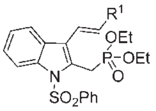
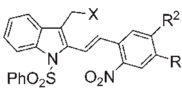
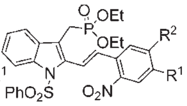
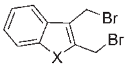
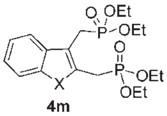
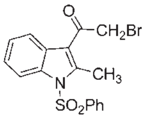
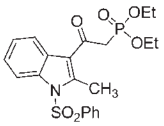
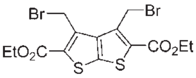
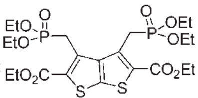
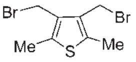
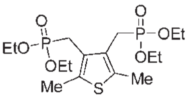
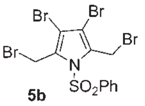
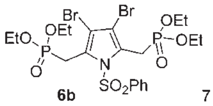
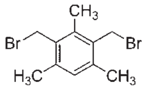
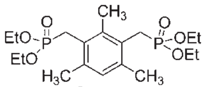
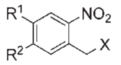
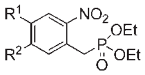
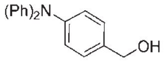
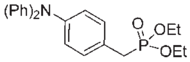
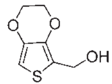
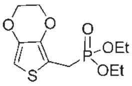
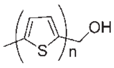
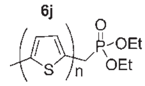
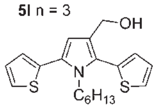
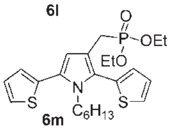
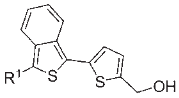
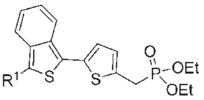
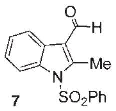
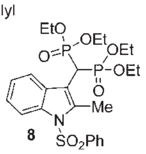
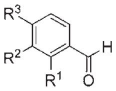
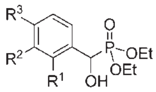
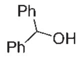
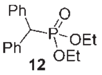
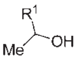
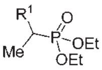
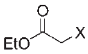
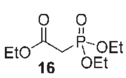
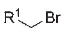
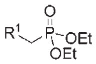
Table 1. $ZnBr_2$-Mediated Michaelis−Arbuzov Reaction of Arylmethyl Halides/Alcohols and Aryl Aldehydes

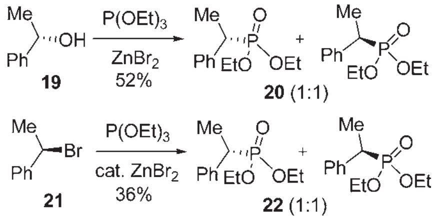
entry	substrate	product	condition	yield (%)
1				
	3a R^1 = SPh, X = Br	**4a-g**	3 h[a]	85
	3a' R^1 = SPh, X = Cl		10 h[c]	75
	3b R^1 = SPh, X = OH		10 h[b]	78
	3c R^1 = Me, X = Br		3 h[a]	90
	3c' R^1 = Me, X = Cl		4 h[c]	80
	3d R^1 = Me, X = OH		10 h[b]	75
	3e R^1 = COCH$_3$, X = Br		5 h[a]	85
	3f R^1 = CO$_2$Et, X = Br		7 h[a]	80
	3g R^1 = CN, X = Br		10 h[a]	70
2				
	3h R^1 = CO$_2$Et	**4h-j**	5 h[a]	85
	3i R^1 = CO$_2$Me		5 h[a]	83
	3j R^1 = COMe		5 h[a]	0
3				
	3k R^1, R^2 = H, X = Br	**4k**	5 h[a]	82
	3l R^1, R^2 = OMe, X = Br	**4l**	5 h[a]	86
	3l' R^1, R^2 = OMe, X = Cl		12 h[c]	0
4				
	3m X = NSO$_2$Ph	**4m**	10 h[b]	70
	3n X = S	**4n**	6 h[b]	80
5	 **3o**	 **4o**	4 h[a]	0
6	 **3p**	 **4p**	7 h[b]	85
7	 **5a**	 **6a**	7 h[b]	82
8	 **5b**	 **6b**	7 h[b]	73
9	 **5c**	 **6c**	2 h[b]	75
10				
	5d R^1, R^2 = H, X = Br	**6d-h**	5 h[a]	90
	5d' R^1, R^2 = H, X = Cl		10 h[c]	0
	5d'' R^1, R^2 = H, X = OH		10 h[c]	0
	5e R^1, R^2 = OMe, X = Br		4 h[a]	84
	5e' R^1, R^2 = OMe, X = Cl		10 h[c]	0
	5e'' R^1, R^2 = OMe, X = OH		10 h[c]	0
	5f R^1 = F, R^2 = H, X = Br		5 h[a]	85
	5g R^1 = H, R^2 = F, X = Br		4 h[a]	91
	5h R^1 = Cl, R^2 = H, X = Br		5 h[a]	88
11	 **5i**	 **6i**	2 h[c]	75
12	 **5j**	 **6j**	1 h[c]	90
13				
	5k n = 2	**6k**	2 h[c]	91
	5l n = 3	**6l**	2 h[c]	93
14	 **5m**	 **6m**	2 h[c]	80
15				
	5n R^1 = 2-thienyl	**6n-q**	2 h[c]	87
	5o R^1 = *p*-anisyl		2 h[c]	89
	5p R^1 = 9-hexyl-3-carbazolyl		2 h[c]	90
	5q R^1 = *p*-tolyl-3-carbazolyl		2 h[c]	93
16	 **7**	 **8**	3 h[d]	85
17				
	9a R^1 = Cl, R^2 = H, R^3 = Cl	**10a-d**	1 h[d]	91
	9b R^1 = H, R^2 = H, R^3 = Cl		2 h[d]	87
	9c R^1 = H, R^2 = H, R^3 = Br		2 h[d]	85
	9d R^1 = H, R^2 = NO$_2$, R^3 =H		4 h[d]	80
18	 **11**	 **12**	4 h[c]	89
19				
	13a R^1 = Ph	**14a** R^1 = Ph	3 h[c]	85
	13b R^1 = 2-thienyl	**14b** R^1 = 2-thienyl	5 h[c]	63
20				
	15a X = Br	**16**	4 h[a]	93
	15b X = Cl		10 h[a]	0
21				
	17a R^1 = *n*-C$_5$H$_{11}$	**18a** R^1 = *n*-C$_5$H$_{11}$	10 h[a]	0
	17b R^1 = *n*-C$_4$H$_9$	**18b** R^1 = *n*-C$_4$H$_9$	10 h[a]	0

[a] The reaction was performed using bromo compound (1 mmol), $ZnBr_2$ (0.2 mmol), and P(OEt)$_3$ (1.2 mmol) in dichloromethane. [b] The reaction was performed using bromo compound (1 mmol), $ZnBr_2$ (0.4 mmol), and P(OEt)$_3$ (2.5 mmol) in dichloromethane. [c] The reaction was performed using benzylic alcohol/benzyl chloride (1 mmol), $ZnBr_2$ (1.1 mmol), and P(OEt)$_3$ (5 mmol). [d] The reaction was performed using aldehyde (1 mol), $ZnBr_2$ (1.1 mmol), and P(OEt)$_3$ (1.3 mmol) in DCE.

failed to produce the expected phosphonate ester **4o** and instead led to the isolation of the respective debrominated methylindole (entry 5). The Michaelis–Arbuzov reaction was found to be successful with bis(bromomethyl) compounds as well (entries 4 and 6–9). The reaction of 1-bromomethyl-2-nitroarenes **5d–h** with triethyl phosphite in the presence of 20 mol % of ZnBr$_2$ furnished the respective phosphonate esters **6d–h** in excellent yields (entry 10). The ZnBr$_2$-mediated Michaelis–Arbuzov reaction of 1-chloromethyl-2-nitroarene **5d′**/**5e′** as well as 1-hydroxymethyl-2-nitroarene **5d″**/**5e″** was found to be unsuccessful (entry 10). Recently, a facile Lewis-acid mediated arylation of activated benzylic alcohols was achieved in good yields.[20] Hence, we propose to do a Lewis acid mediated Michaelis–Arbuzov reaction of benzylic alcohols. Accordingly, the interaction of electron-rich heteroarylmethyl alcohols with triethyl phosphite in the presence of 1.1 equiv of anhyd ZnBr$_2$ led to the formation of corresponding phosphonate esters in 75–93% yields (entries 11–15). The interaction of indole-3-carboxaldehyde **7** with triethyl phosphite in the presence of 1.1 equiv of ZnBr$_2$ at room temperature furnished diphosphonate ester **8** in 85% yield (entry 16). Under identical conditions, the reaction of aryl aldehydes **9a–d** led to the isolation of respective α-hydroxyphosphonate esters **10a–d** in 80–91% yields (entry 17). Gratifyingly, the interaction of benzhydrol **11** with triethyl phosphite in the presence of 1.1 equiv of ZnBr$_2$ at room temperature led to the isolation of known phosphonate ester **12** in 89% yield (entry 18). The reaction was found to be successful with secondary benzylic alcohols as well (entry 19). As expected, the reaction of ethyl bromoacetate **15a** with triethyl phosphite in the presence of 20 mol % of ZnBr$_2$ at room temperature led to the isolation of triethyl phosphonoacetate **16** in 93% yield. However, under identical conditions, the reaction of ethyl chloroacetate **15b** with triethyl phosphite in the presence of ZnBr$_2$ failed to produce the phosphonate ester **16** (entry 20). Finally, the Lewis acid mediated Michaelis–Arbuzov reaction was also found to be unsuccessful with *n*-hexyl bromide/*n*-butyl bromide (entry 21).

To verify the mechanism of the Lewis acid mediated Michaelis–Arbuzov reaction, (*S*)-(−)-1-phenylethanol **19**/(*R*)-(+)-1-phenylbromoethane **21**[21] was reacted with triethyl phosphite in the presence of ZnBr$_2$ (Scheme 3). Usual workup and purification followed by HPLC analysis (see the Supporting Information) indicated the formation of racemic phosphonate esters **20** and **22**. Hence, it may be concluded that the LA-mediated Michaelis–Arbuzov reaction of benzylic bromide/alcohol involves only an S$_N$1-type mechanism.

Scheme 3. Lewis Acid-Mediated Michaelis–Arbuzov Reaction of Chiral Benzylic Alcohol/Bromide



In summary, for the first time, LA-mediated Michaelis–Arbuzov reaction of arylmethyl as well as heteroarylmethyl halides/alcohols was achieved at room temperature. The reaction has been successfully extended to the synthesis of α-hydroxyphosphonate esters as well. The 2-nitroaryl phosphonate esters reported herein may find application in the synthesis of alkaloids.[22] The various types of heteroarylmethyl phosphonates reported herein may be regarded as crucial intermediates for the synthesis of conjugated vinylenes.[23]

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Supporting Information Available. Experimental procedure along with characterization data and ^{1}H and ^{13}C NMR spectra of representative phosphonate esters. This material is available free of charge via the Internet at http://pubs.acs.org.

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