Environmentally-Friendly Wohl–Ziegler Bromination: Ionic-Liquid Reaction and Solvent-Free Reaction

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Abstract: Environmentally-friendly Wohl–Ziegler bromination of benzylic methyl groups was successfully carried out in ionic-liquid and solvent-free systems, to produce the corresponding benzylic bromides in good to moderate yields.

Key words: Wohl–Ziegler bromination, benzylic bromide, *N*-bromosuccinimide (NBS), 2,2′-azobis(isobutyronitrile) (AIBN), benzoyl peroxide, ionic-liquid, solvent-free

The Wohl–Ziegler bromination with *N*-bromosuccinimide (NBS) and a catalytic amount of benzoyl peroxide or 2,2′-azobis(isobutyronitrile) (AIBN) as initiator is a very useful reaction for the selective bromination of benzylic hydrogens under neutral conditions.[1] Therefore, it has been widely used for the preparation of benzylic bromides in natural products and in supramolecular compound syntheses, such as fullerene precursor, dendrimer core, etc.[2] The reaction is generally quite specific at the benzylic position. However, highly toxic carbon tetrachloride has been used as a solvent generally, in spite of the serious health hazards involved. Recently, environmentally-friendly organic synthesis has become very important and popular, such as solvent-free organic synthesis, especially those using microwaves,[3] or organic reactions in room temperature ionic liquids as new reaction media,[4,5] aiming toward green chemistry. Here, as a part of our study on environmental friendly organic synthesis via radical reactions,[6] we would like to report on the Wohl–Ziegler bromination of various benzylic hydrogens with NBS initiated by benzoyl peroxide or AIBN in ionic liquid and solvent-free reactions. Upto now, the synthetic study of radical reactions in ionic liquid[7] and of solvent-free reactions has been quite limited, since it is difficult to control the reactions, especially radical chain reactions. Thus, the Wohl–Ziegler bromination with NBS in the presence of a catalytic amount of benzoyl peroxide or AIBN was carried out in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), which is a typical room temperature ionic liquid, and under solvent-free conditions. These reactions proceeded effectively as shown in Table 1.

The conversion of benzylic methyl groups to benzylic bromides bearing various kinds of substituents at the *p*-position, such as *p*-CO_2Et, *p*-Br, *p*-NO_2, *p*-CN, *p*-PhCO, *p*-CH_3SO_2, *p*-$PhSO_3$, *p*-*t*-Bu, proceeded effectively in an ionic liquid solvent and under solvent-free conditions, respectively, and the same reactivities as those in carbon tetrachloride were observed. However, in *p*-methoxytoluene, ionic bromination of the aromatic ring with NBS in ionic-liquid solvent occurred, while bromination of benzylic methyl groups in *p*-methoxytoluene occurred predominantly under solvent-free conditions as in carbon tetrachloride. Today, the ionic bromination of an aromatic ring with NBS is known,[8] and these results indicate that a polar solvent such as ionic liquid accelerates the ionic bromination of the aromatic ring with NBS. The same tendency was also observed in benzylic bromination of 1-methylnaphthalene and 2-methylnaphthalene. Thus, benzylic bromination of electron-deficient aromatics in ionic liquid proceeds effectively, while that of electron-rich aromatics in ionic liquid does not proceed and, instead, ionic bromination of the aromatic ring occurred mainly. Under solvent-free conditions, the corresponding benzylic bromides were obtained effectively in both reactions, initiated by benzoyl peroxide and AIBN. Benzylic hydrogens bearing a carbonyl, lactone, or methanesulfonyl group were also converted to the corresponding benzylic bromides effectively in [bmim]PF_6 or under solvent-free conditions. Here, 1-butyl-3-methylimidazolium hexafluorophosphate can be used repeatedly, and the yields of benzylic bromides in the reactions of ethyl *p*-toluate with NBS initiated by benzoyl peroxide and of ethyl *p*-toluate with NBS initiated by AIBN, respectively, do not change and remain high as shown in Table 2.

Allylic monobromination and dibromination of diethyl isopropylidenemalonate with NBS and a catalytic amount of benzoyl peroxide or AIBN under solvent-free conditions also proceeds effectively to generate the corresponding bromomethyl and bis(bromomethyl) compounds **1** and **2** in moderate yields, respectively, as shown in Table 3.

Thus, the present Wohl–Ziegler bromination of benzylic methyl groups in ionic-liquid and solvent-free systems, should be a useful and environmentally-friendly method for the preparation of the corresponding benzylic bromides in good to moderate yields, respectively.

Typical Procedure 1: To a mixture of ethyl *p*-toluate (6 mmol), NBS (6.3 mmol), and benzoyl peroxide (0.24 mmol) was added 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6, 2 mL) as a solvent. The mixture was heated at 90 °C under an argon atmosphere. The reaction was monitored by TLC until the starting

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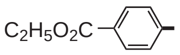
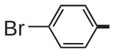
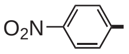
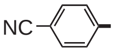
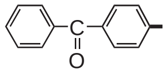
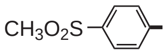
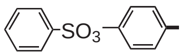
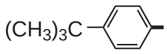
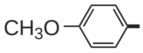
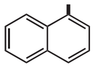
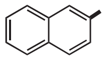
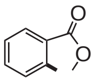
Table 1 Wohl–Ziegler Bromination with [bmim]PF_6 Solvent and Solvent-free System

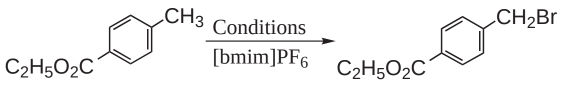
$$\text{Ar-CH}_3 \xrightarrow[\text{[bmim]PF}_6\text{ or Solvent-free}]{\text{Conditions (}\mathbf{A}\text{ or }\mathbf{B}\text{)}} \text{Ar-CH}_2\text{Br}$$

Condition **A**: NBS (1.05 equiv), $(PhCO_2)_2$ (0.04 equiv), 90–95 °C
Condition **B**: NBS (1.2 equiv), AIBN (0.1 equiv), 60–65 °C

Ar–	[bmim]PF_6 Yields (%)		Solvent-free Yields (%)	
	A	B	A	B
	76	79	68	73
	72	72	59	50
	70	61	69	75
	72	82	63	78
	77	81	68	75
	75	77	73	73
	77	80	70	76
	70	78	65	58
	5 (95)[a]	trace (88)[a]	64 (trace)[a]	55 (trace)[a]
	3 (73)[b]	7 (57)[b]	73 (1)[b]	83 (trace)[b]
	trace (> 99)[c]	trace (> 99)[c]	52 (17)[c]	21 (72)[c]
	26	3	90	89

[a] Yield of 3-bromo-4-methoxytoluene.
[b] Yield of 4-bromo-1- methylnaphthalene.
[c] Yield of 1-bromo-2-methylnaphthalene.

Table 2 Uses of Recycled [bmim]PF_6

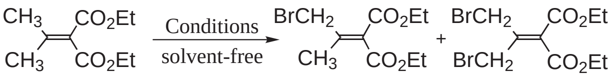


Condition **A**: NBS (1.05 equiv), $(PhCO_2)_2$ (0.04 equiv), 90–95 °C					
Regeneration	1	2	3	4	5
Yield (%)	76	74	72	69	73
Condition **B**: NBS (1.2 equiv), AIBN (0.1 equiv), 60–65 °C					
Regeneration	1	2	3	4	5
Yield (%)	79	79	78	78	78

ethyl *p*-toluate was consumed completely. After one hour, ether was added to the reaction mixture and extracted 5 times (5 mL × 5). The combined ether was evaporated, and the residue was chromatographed on silica gel (eluent, hexane–ethyl acetate = 5:1) to obtain ethyl α-bromo-*p*-toluate in 76% yield. Used [bmim]PF_6 was washed with water (5 mL), dried under reduced pressure with a vacuum pump at 70 °C for 5 h, and repeatedly used for the same reaction.

Typical Procedure 2: To a flask were added phthalide (6 mmol), NBS (7.2 mmol), and AIBN (0.6 mmol) under an argon atmosphere. The mixture was well mixed with stirring for 2 min. Then the mixture was heated at 60 °C until the starting phthalide was consumed completely. After one hour, diethyl ether (15 mL) was added to the mixture, and the obtained mixture was filtered to remove succinimide. The filtrate was evaporated and the residue was chromatographed on silica gel (eluent: hexane–ethyl acetate = 1:1) to give 3-bromophthalide in 89% yield.

Table 3 Monobromination and Dibromination of Diethyl Isopropylidenemalonate with Solvent-Free System



1 2

NBS	Initiator	Conditions	Yields (%)	
			1	**2**
monobromination				
1.05 equiv	$(PhCO_2)_2$: 0.04 equiv	90 °C, 20 min	67	12
1.2 equiv	AIBN: 0.1 equiv	65 °C, 2 h	76	15
dibromination				
2.1 equiv	$(PhCO_2)_2$: 0.08 equiv	90 °C, 2 h	13	43
2.4 equiv	AIBN: 0.2 equiv	65 °C, 4 h	7	62

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