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PHOSPHONIUM CHLORIDE AS A NON-VOLATILE CHLORINATING REAGENT: PREPARATION AND REACTION IN NO SOLVENT OR IONIC LIQUID

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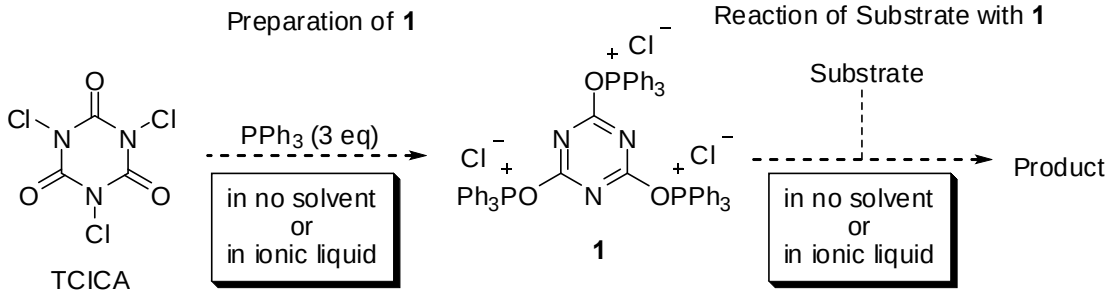
Abstract – Reaction of triphenylphosphine with trichloroisocyanuric acid in no solvent or an ionic liquid gave the corresponding phosphonium chloride, which can be used as a cheap and safe chlorinating reagent. Conversion of hydroxyheterocycles to chloroheterocycles, carboxylic acids to carboxylic acid chlorides, and primary amides to nitriles were accomplished by using the phosphonium chloride in excellent to good yields.

Chlorination of nitrogen-containing π-deficient heterocycles (abbreviated as heterocycles) is one of the important methods in heterocyclic chemistry because chloroheterocycles are frequently used as useful synthetic intermediates. Phosphorus oxychloride ($POCl_3$) and phosphorus pentachloride (PCl_5) are widely used for a powerful reagent for the chlorination of many hydroxyheterocycles.[1-6] However, since $POCl_3$ and PCl_5 are highly reactive with water, the uses of them are troublesome at the work-up process. It was found that phosphonium chlorides prepared by reaction of triphenylphosphine (PPh_3) with *N*-chloro compounds can be used as a chlorinating reagent.[7-12] Especially, the reagent **1** which is prepared by reaction of PPh_3 and trichloroisocyanuric acid (TCICA), react as a useful substitute for $POCl_3$ or PCl_5.[12] This reagent **1** is usually used in an appropriate solvent, which is chosen by reactivity of the substrate. However, removal of a solvent which have high boiling point is hard at post-treatment. Since recent studies[13] show that certain phosphonium salts act as ionic liquids due to their low melting points. From these points of view, development of a solvent-free preparation and reaction of **1** would be useful. In this paper, preparation and reaction of **1** in no solvent or an ionic liquid was carried out as shown in Scheme 1.

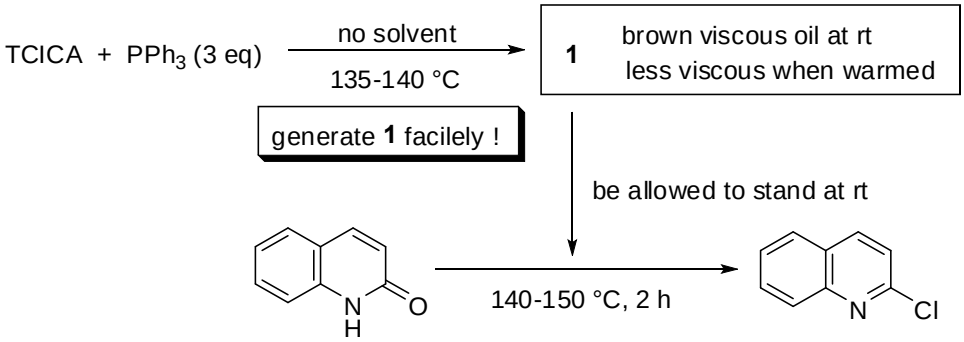
This paper is dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday



Scheme 1. Overview of this work

At first, preparation of **1** under solvent-free condition was examined. A mixture of TCICA and PPh_3 was warmed slowly by heating bath. PPh_3 melted at 100 °C, and TCICA was vigorously reacted with PPh_3 at 135-140 °C to form **1**. The resulting **1** at room temperature is too viscous to stir by a magnetic stirrer. However, **1** becomes less viscous enough to stir when warmed at 100 °C or above. Thus, it is expected that **1** can be used as a non-volatile and solvent-free available chlorinating reagent. As shown in Table 1, reaction of the substrate, 2(1*H*)-quinolinone with **1** under several conditions were carried out to optimize the condition.

Table 1. Preparation of **1** followed by reaction with 2(1*H*)-quinolinone under solvent-free condition



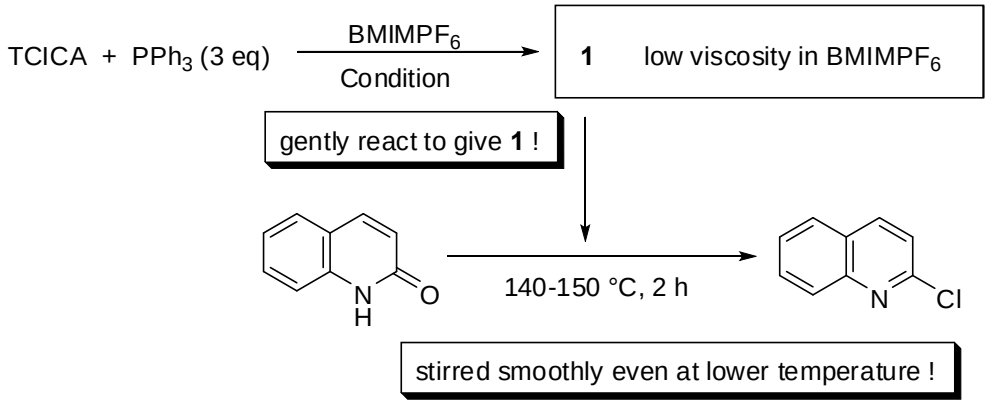
Entry	**1**		Yield (%)
	Amount (eq)	Be allowed to stand at rt for (days)	
1	1	0	54
2	1	8	50
3	1	24	42
4	1.5	0	79
5	2	0	86

The substrate was added to **1** (1 eq) and heated at 140-150 °C for 2 h to give the corresponding chlorinated product, 2-chloroquinoline in 54% yield (Entry 1). In order to clarify the stability of **1**,

reaction of 2(1*H*)-quinolinone with **1** (1 eq) which was allowed to stand at room temperature for 8 and 24 days after preparation was carried out, and 2-chloroquinoline was obtained in 50% and 42% yields, respectively (Entries 2 and 3). These results indicate that **1** is stable for at least a few days at room temperatue. Next, chlorination of 2(1*H*)-quinolinone with varying amounts of **1** was carried out. When excess **1** (1.5 eq and 2 eq) was used, the products were obtained in 79% and 86% yields, respectively (Entries 4 and 5). As summarized in Table 1, the phosphonium chloride **1**, which is prepared from solvent-free reaction of PPh_3 with TCICA, can be used as a non-volatile chlorinating reagent. It should be noted that reaction using **1** in no solvent can be manipulated at arbitrary temperature (for example, high temperature such as 140-150 °C) since **1** has extremely low vapor pressure.

Reaction of PPh_3 with TCICA under solvent-free condition is a useful method to facilely generate **1**. However, this method in a large scale may be troublesome since TCICA vigorously react with PPh_3 at 135-140 °C. So in order to generate **1** gently and to lower the viscosity of **1**, preparation and reaction of **1** in room temperature ionic liquids (RTILs) was carried out as shown in Table 2.

Table 2. Preparation of **1** followed by reaction with 2(1*H*)-quinolinone in $BMIMPF_6$



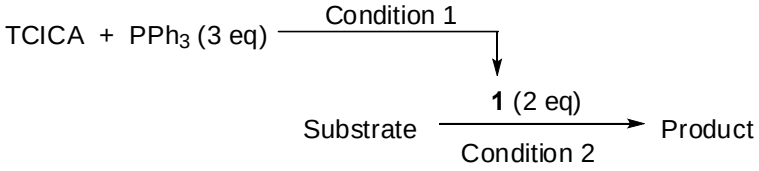
Entry	Amount of **1** (eq)	Condition	Yield (%)
1	1	rt, 18 h	43
2	1	75-80 °C, 1 h	47
3	1	120 °C[1)]	48
4	2	rt, 24 h	67
5	2	75-80 °C, 1 h	84
6	2	115-120 °C, 15 min	93
7	2	130 °C[1)]	84
8	2	140-150 °C[1)]	78

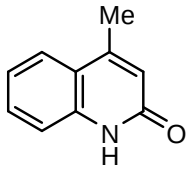
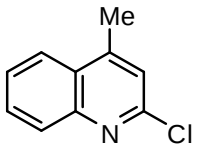
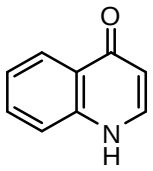
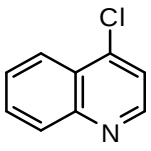
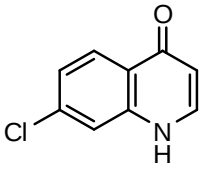
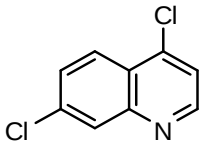
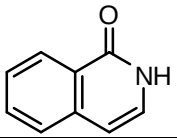
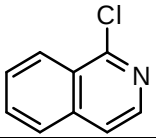
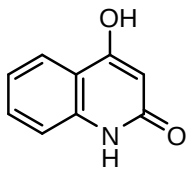
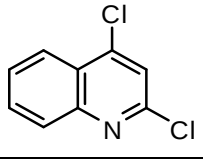
1) A mixture of PPh_3 and TCICA was heated at this temperature until TCICA was quickly reacted with PPh_3.

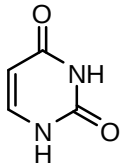
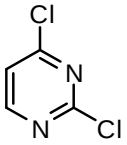
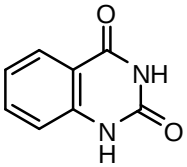
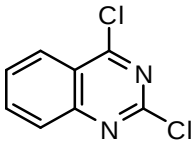
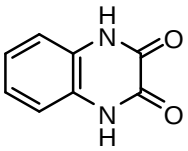
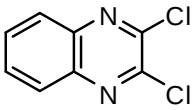
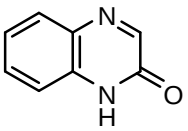
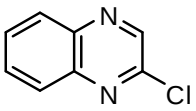
A mixture of PPh_3 and TCICA in $BMIMPF_6$ was stirred at several temperatures followed by reaction with 2(1*H*)-quinolinone at 140-150 °C for 2 h. The reaction time was reduced as the reaction temperature rose (Entries 1-4). When 2 equivalents of **1** was used, the yield of 2-chloroquinoline was improved (Entries 5-9). From the results shown in Table 1 and 2, it was found that preparation of **1** in $BMIMPF_6$ is effective in a large reaction scale (10 mmol of **1** or above) since reaction of PPh_3 with TCICA proceeds gently by using $BMIMPF_6$.

Chlorination of hydroxyazines and hydroxydiazines using **1** in no solvent or $BMIMPF_6$ was carried out in order to find the generality of reaction (Table 3). Azines and diazines are well known to be reactive with nucleophiles at α- or γ-position to the ring nitrogen. α-Hydroxy compound (Entries 1, 2, 7, 8, 17, and 18), γ-hydroxy compound (Entries 3-6), and dihydroxy compound (Entries 9-16) were used as substrates.

Table 3. Chlorination of quinolinones and isoquinolinones using **1**



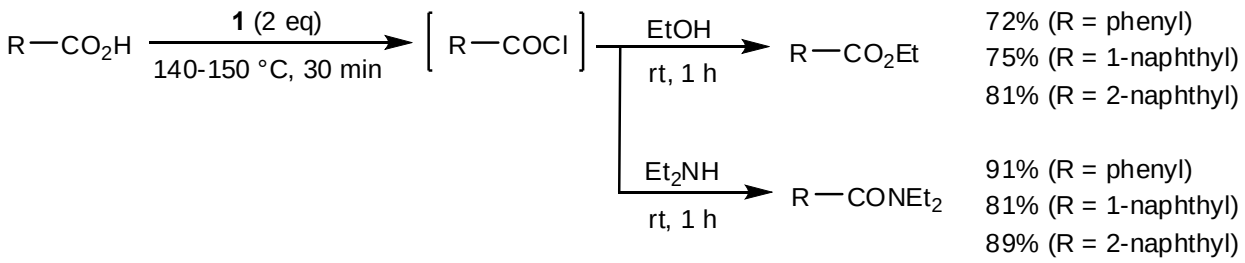
Entry	Substrate	Solvent	Condition 1 Condition 2	Product	Yield (%)
1		No solvent	130 °C[1)] 140-150 °C, 2 h		85
2		$BMIMPF_6$	135 °C[1)] 140-150 °C, 2 h		75
3		No solvent	135 °C[1)] 140-150 °C, 2 h		65
4		$BMIMPF_6$	75-80 °C, 1 h 140-150 °C, 2 h		65
5		No solvent	135 °C[1)] 140-150 °C, 2 h		66
6		$BMIMPF_6$	135 °C[1)] 140-150 °C, 2 h		83
7		No solvent	135 °C[1)] 140-150 °C, 2 h		65
8		$BMIMPF_6$	135 °C[1)] 140-150 °C, 2 h		57
9		No solvent	135-140 °C[1)] 140-150 °C, 2 h		62
10		$BMIMPF_6$	75-80 °C, 1 h 140-150 °C, 2 h		45

11		No solvent	135 °C[1)] 140-150 °C, 2 h		60
12		$BMIMPF_6$	130 °C[1)] 140-150 °C, 2 h		59
13		No solvent	130 °C[1)] 170-180 °C, 2 h		59
14		$BMIMPF_6$	135 °C[1)] 170-180 °C, 2 h		38
15		No solvent	125 °C[1)] 140-150 °C, 2 h		41
16		$BMIMPF_6$	130 °C[1)] 140-150 °C, 4 h		46
17		No solvent	140 °C[1)] 140-150 °C, 2 h		67
18		$BMIMPF_6$	130 °C[1)] 140-150 °C, 2 h		66

1) A mixture of PPh_3 and TCICA was heated at this temperature until TCICA was quickly reacted with PPh_3.

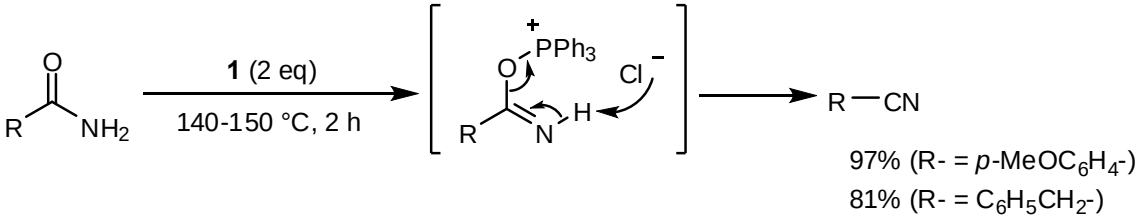
A mixture of the substrate and **1**, which was prepared by reaction of PPh_3 with TCICA at 135-140 °C for 15 min (no solvent) or 75-80 °C for 1 h (in $BMIMPF_6$), was heated at 140-150 °C for 2 h. All substrates reacted with **1** in no solvent or $BMIMPF_6$ to give the corresponding chlorinated products in high to moderate yields.

Activation of carboxylic acids using **1** followed by addition of nucleophiles were carried out as shown in Scheme 2. Carboxylic acids (benzoic acid, 1-naphthoic acid, and 2-naphthoic acid) was reacted with **1** (2 eq) at 140-150 °C for 30 min to afford the corresponding carboxylic acid chlorides, which was treated with ethanol at room temperature for 1 h to give the corresponding carboxylic acid ethyl esters. Amidation of carboxylic acids were examined by a similar method. Carboxylic acid chlorides generated from carboxylic acids reacted with diethylamine at room temperature to give carboxylic acid diethylamides in excellent yields.



Scheme 2. Generation of acyl chlorides using **1** followed by addition of ethanol or diethylamine

Dehydration of primary amides using **1** was carried out (Scheme 3). *p*-Methoxybenzamide as an aromatic amide and phenylacetamide as an aliphatic amide were used as substrates. Reaction of the substrates with **1** at 140-150 °C for 2 h gave the desired nitriles in excellent yields.



Scheme 3. Dehydration of primary amides using **1**

In conclusion, we have clarified that the phosphonium chloride **1** can be generated in no solvent or $BMIMPF_6$ to perform as a useful substitute for conventional chlorinating reagents such as $POCl_3$ or PCl_5.

EXPERIMENTAL

All melting points were not corrected. ^{1}H-NMR spectra were measured with Hitachi R-90H spectrometer (90 MHz) using tetramethylsilane as an internal standard.

Preparation and reaction of ((1,3,5-triazine-2,4,6-triyl)tris(oxy))tris(triphenylphosphonium) chloride (**1**) under solvent-free condition (General procedure): In a 50 mL of recovery flask equipped with reducing joint and balloon, a mixture of TCICA (317 mg, 1.36 mmol) and PPh_3 (1050 mg, 4.00 mmol) was warmed slowly by heating bath. PPh_3 melted at 100 °C, and TCICA was vigorously reacted with PPh_3 at 135-140 °C followed by stirring for 5 min to give brown oil, **1.** 2(1*H*)-Quinolinone (295 mg, 2.03 mmol) was added to **1** and heated at 140-150 °C for 2 h. White solids were sublimed to adhere to the surface of reducing joint. Et_2O was added to the reaction mixture (including the sublimed solids) and basified with triethylamine. After Et_2O layer was separated for 3 times, the Et_2O solution was combined and concentrated followed by purification with silica gel column chromatography (eluted with hexane-EtOAc (10:1)) to give 2-chloroquinoline (287 mg, 86%).

2-Chloroquinoline: Colorless oil. ^{1}H-NMR ($CDCl_3$), δ: 7.38 (1H, d, J = 8.5 Hz, C^3-H), 7.50-7.90 (3H, m, C^5, C^6, and C^7-H), 8.02 (1H, d, J = 6.2 Hz, C^8-H), 8.10 (1H, d, J = 8.5 Hz, C^4-H).

Preparation and reaction of **1** in $BMIMPF_6$ (General procedure): In a 50 mL of recovery flask equipped with reducing joint and balloon, a mixture of TCICA (315 mg, 1.36 mmol), PPh_3 (1051 mg, 4.01 mmol), and $BMIMPF_6$ (3 mL) was warmed at 75-80 °C until TCICA was completely consumed (for 1 h) to give

$BMIMPF_6$ solution of **1**. 2(1*H*)-Quinolinone (290 mg, 2.00 mmol) was added to $BMIMPF_6$ solution of **1** and heated at 140-150 °C for 2 h. White solids were sublimed to adhere to the surface of reducing joint. Et_2O was added to the reaction mixture (including the sublimed solids) and basified with triethylamine. After Et_2O layer was separated for 3 times, the Et_2O solution was combined and concentrated followed by purification with silica gel column chromatography (eluted with hexane-EtOAc (8:1)) to give 2-chloroquinoline (275 mg, 84%).

2-Chloro-4-methylquinoline: Slight yellow solids. Mp 52.5 °C (lit.,[14] 55-57 °C). ^{1}H-NMR ($CDCl_3$), δ: 7.24 (1H, s, C^3-H), 7.43-7.83 (2H, m, C^6 and C^7-H), 7.83-8.11 (2H, m, C^5 and C^8-H).

4-Chloroquinoline: Colorless oil. ^{1}H-NMR ($CDCl_3$), δ: 7.49 (1H, d, J = 4.8 Hz, C^3-H), 7.59-7.95 (2H, m, C^6 and C^7-H), 7.95-8.42 (2H, m, C^5 and C^8-H), 8.78 (1H, d, J = 4.8 Hz, C^2-H).

4,7-Dichloroquinoline: White solids. Mp 86.9 °C (lit.,[15] 86.4-87.4 °C). ^{1}H-NMR ($CDCl_3$), δ: 7.48 (1H, d, J = 4.7 Hz, C^3-H), 7.50-7.71 (1H, m, C^6-H), 7.99-8.31 (1H, m, C^5-H), 8.12 (1H, s, C^8-H), 8.77 (1H, d, J = 4.7 Hz, C^2-H).

1-Chloroisoquinoline: Slight yellow solids. Mp 30.1 °C (lit.,[16] 35-37 °C). ^{1}H-NMR ($CDCl_3$), δ: 7.42-7.98 (4H, m, C^4, C^5, C^6, and C^7-H), 8.13-8.47 (2H, m, C^3 and C^8-H).

2,4-Dichloroquinoline: Pale yellow solids. Mp 62.3 °C (lit.,[17] 66-67 °C). ^{1}H-NMR ($CDCl_3$), δ: 7.51 (1H, s, C^3-H), 7.59-7.91 (2H, m, C^6 and C^7-H), 7.91-8.30 (2H, m, C^5 and C^8-H).

2,4-Dichloropyrimidine: White solids. Mp 58-59 °C (lit.,[18] 60-61 °C). ^{1}H-NMR ($CDCl_3$), δ: 7.33 (1H, d, J = 5.3 Hz, C^5-H), 8.52 (1H, d, J = 5.3 Hz, C^6 -H).

2,4-Dichloroquinazoline: White solids. Mp 120 °C (lit.,[19] 120-121 °C). ^{1}H-NMR ($CDCl_3$), δ: 7.51 (1H, s, C^3-H), 7.59-7.91 (2H, m, C^6 and C^7-H), 7.91-8.30 (2H, m, C^5 and C^8-H).

2,3-Dichloroquinoxaline: White solids. Mp 157.2 °C (lit.,[20] 152-153 °C). ^{1}H-NMR ($CDCl_3$), δ: 7.60-7.90 (2H, m, C^6 and C^7-H), 7.90-8.17 (2H, m, C^5 and C^8-H).

2-Chloroquinoxaline: White solids. Mp 47.1 °C (lit.,[21] 47-47.5 °C). ^{1}H-NMR ($CDCl_3$), δ: 7.60-7.90 (2H, m, C^6 and C^7-H), 7.90-8.30 (2H, m, C^5 and C^8-H), 8.78 (1H, s, C^3-H).

Ethyl benzoate: Colorless liquids. ^{1}H-NMR ($CDCl_3$), δ: 1.40 (3H, t, J = 7.1 Hz, CH_3), 4.38 (2H, q, J=7.1 Hz, CH_2), 7.28-7.71 (3H, m, phenyl-H), 7.92-8.19 (2H, m, phenyl-H).

Ethyl 1-naphthoate: Colorless liquids. ^{1}H-NMR ($CDCl_3$), δ: 1.45 (3H, t, J = 7.1 Hz, CH_3), 4.47 (2H, q, J = 7.1 Hz, CH_2), 7.31-7.73 (3H, m, aromatic-H), 7.73-8.27 (3H, m, aromatic-H), 8.90 (1H, d, J = 8.2 Hz, aromatic-H).

Ethyl 2-naphthoate: Colorless liquids. ^{1}H-NMR ($CDCl_3$), δ: 1.44 (3H, t, J = 7.1 Hz, CH_3), 4.44 (2H, q, J = 7.1 Hz, CH_2), 7.38-7.70 (2H, m, aromatic-H), 7.70-8.20 (4H, m, aromatic-H), 8.60 (1H, s, aromatic-H).

N,*N*-Diethylbenzamide: Slight yellow liquids. ^{1}H-NMR ($CDCl_3$), δ: 1.17 (6H, t, J = 6.8 Hz, $CH_3 \times 2$), 3.40

(4H, brs, $CH_2 \times 2$), 7.37 (5H, s, phenyl-H).

N,*N*-Diethyl-1-naphthamide: Slight yellow oil. ^{1}H-NMR ($CDCl_3$), δ: 0.99 (3H, t, J = 7.1 Hz, CH_3), 1.37 (3H, t, J = 7.1 Hz, CH_3), 3.10 (2H, q, J = 7.1 Hz, CH_2), 3.69 (2H, brs, CH_2), 7.28-7.64 (4H, m, aromatic-H), 7.64-8.00 (3H, m, aromatic-H).

N,*N*-Diethyl-2-naphthamide: Slight yellow oil. ^{1}H-NMR ($CDCl_3$), δ: 1.20 (6H, t, J = 6.9 Hz, $CH_3 \times 2$), 3.43 (4H, brs, $CH_2 \times 2$), 7.30-7.66 (3H, m, aromatic-H), 7.66-8.01 (4H, m, aromatic-H).

4-Methoxybenzonitrile: White solids. Mp 56.1 °C (lit.,[22] 55-57 °C). ^{1}H-NMR ($CDCl_3$), δ: 3.86 (3H, s, CH_3), 6.94 (2H, d, J = 8.8 Hz, aromatic-H), 7.58 (2H, d, J = 8.8 Hz, aromatic-H).

Phenylacetonitrile: Slight yellow liquids. ^{1}H-NMR ($CDCl_3$), δ: 3.74 (2H, s, CH_2), 7.34 (5H, s, phenyl-H).

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