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# Alkylation of 2-(2,4-dichlorophenyl)-3-cyano-6-methyl-4-(1*H*-1,2,4-triazol-1-yl)methylpyridine at the methylene group

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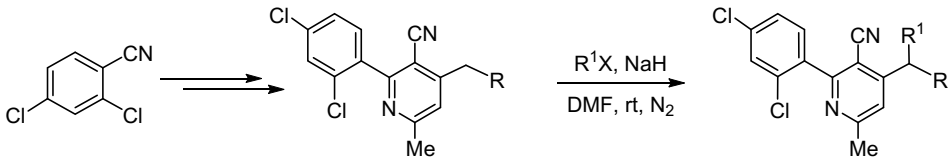



R = 1-triazolyl, 1-imidazolyl
$R^1$ = Me, Et, $CHMe_2$, $CH_2C_6H_{11}$, $CH_2Ph$

The reactivity of the 1-triazolyl- and 1-imidazolyl-substituted methylene groups at position 4 of pyridine ring toward alkyl halides is described. Nitrogen heterocycles attached to the methylene group, as well as a 3-cyano group effectively promoted the alkylation, offering a convenient method for constructing structurally diverse molecules that may present pharmaceutical interest.

**Keywords**: activated methylene compounds, alkyl halides, phenylpyridines, structure–reactivity relationships.

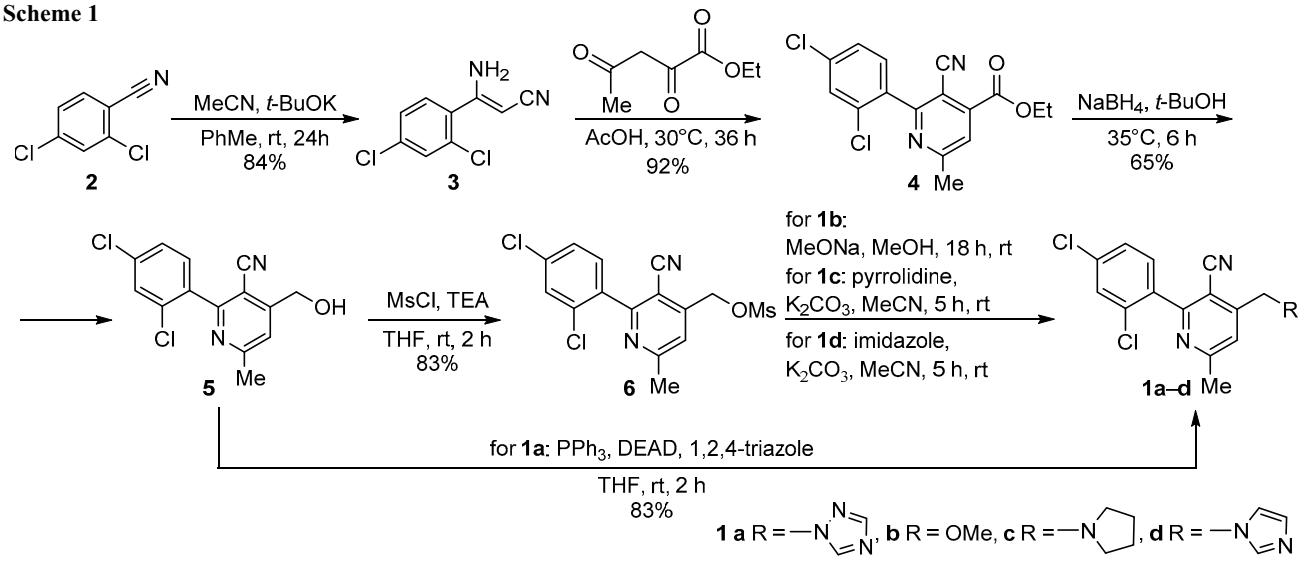
Great advances have been achieved in the field of DPP4 (dipeptidyl peptidase-4) inhibitors as a new class of antihyperglycemic agents during the last decade. Nine DPP4 inhibitors have been approved so far for the treatment of type 2 diabetes, including sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, and related drugs. Clinical use of these medications has shown the advantages of decreased risk of hypoglycemia and potential for weight loss compared to earlier therapies, attracting considerable interest of many researchers toward DPP4 inhibitors.[1] Numerous biaryl scaffolds have recently emerged as a new class of potent and selective DPP4 inhibitors. These include derivatives of 6-phenylbenzimidazole,[2] 1,2-dihydro-4-phenyl-1-isoquinolone,[3] 4-phenylquinoline,[4] 5-phenylpyridopyrimidinedione,[5] 4-phenyl-7-oxopyrrolopyridine,[6] 5-phenylimidazo[1,2-*a*]pyrimidine,[7] and phenylpyridine.[8–10]

In a continuation of search for new DPP4 inhibitors containing biaryl scaffolds, we designed a series of triazole-containing phenylpyridine derivatives. Compound **1a** was used as a critical intermediate for the preparation of the target compounds. While characterizing the structure of compound **1a** by $^1$H NMR spectroscopy in DMSO-$d_6$ solution, hydrogen–deuterium exchange was unexpectedly observed between deuterium oxide and the methylene group linking the pyridine and triazole rings, which pointed to the CH acidity of these methylene protons. This surprising observation provoked our interest to further evaluate the reactivity of this type of 4-substituted phenylpyridine compounds. Thus, we wish to report here the results of alkylation of various 4-substituted phenylpyridine derivatives **1** with some alkyl halides under alkaline conditions.

The synthesis of compound **1a** is illustrated in Scheme 1. 2,4-Dichlorobenzonitrile was treated with MeCN in the presence of *t*-BuOK to form acrylonitrile **3**.[11] Cyclization of compound **3** with ethyl 2,4-dioxovalerate in AcOH gave pyridine **4**.[12] After reduction of compound **4** by $NaBH_4$, the corresponding alcohol **5** was finally converted to compound **1a** by a Mitsunobu reaction with 1,2,4-triazole. $^1$H NMR analysis of compound **1a** revealed that the methylene group singlet at 5.75 ppm was partially deuterated when $D_2O$ was added (Fig. 1). This phenomenon indicated the existence of an acidic methylene group, which prompted us to further explore its reactivity through alkylation reactions.

We began our investigations with the reaction of compound **1a** with MeI (Scheme 2, Table 1, entries 1–7). The reaction was conducted by adding compound **1a** into a suspension of NaH (1.5 equiv) in DMF, followed by the addition of 2 equiv of MeI. After stirring at room temperature for 2 h, the reaction mixture was separated by silica gel column chromatography to give the product in

**Scheme 1**



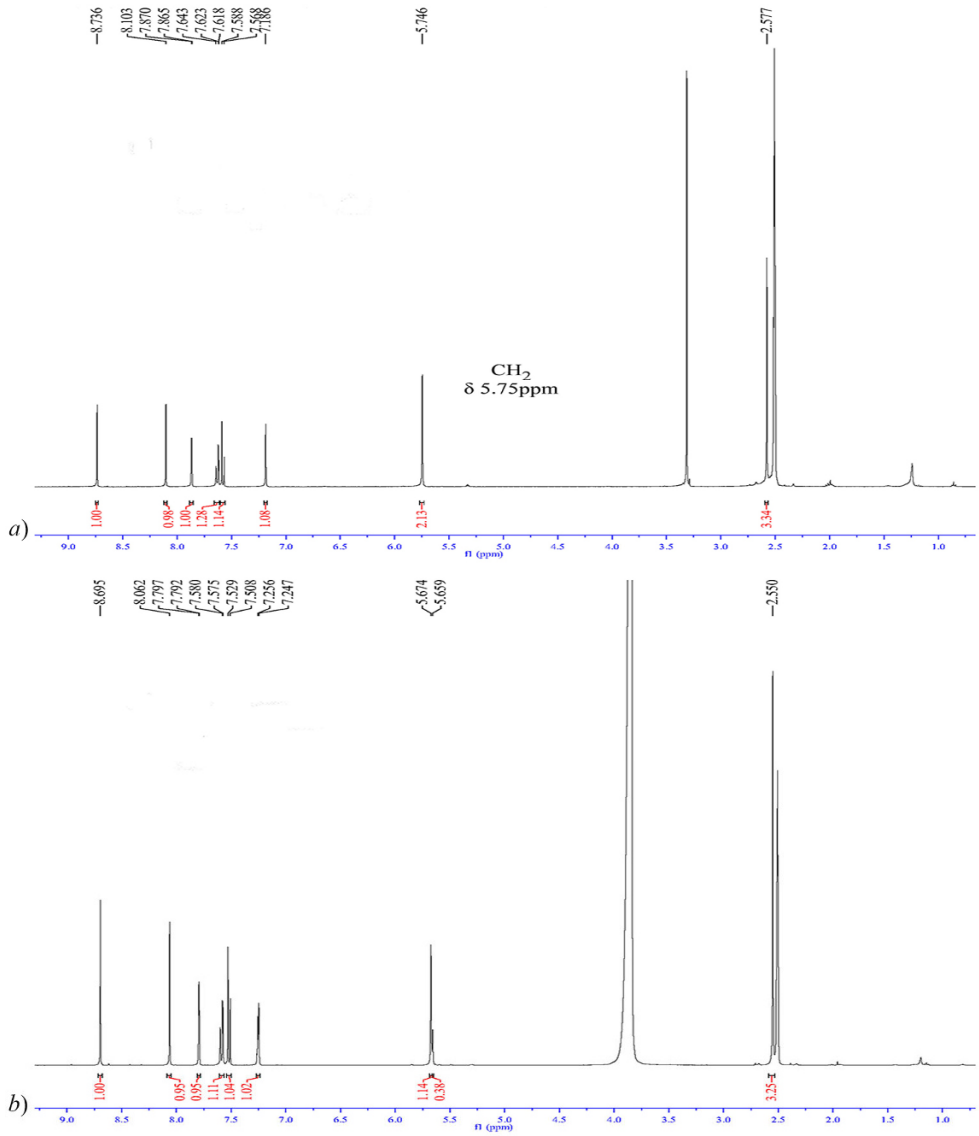
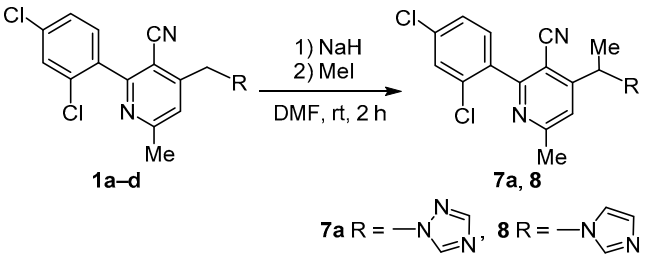




**Figure 1**.[1]H NMR study of compound **1a**. *a*) [1]H NMR spectrum before adding $D_2O$, *b*) [1]H NMR spectrum after maintaining with $D_2O$ for 2 days.

**Scheme 2**




**Scheme 3**

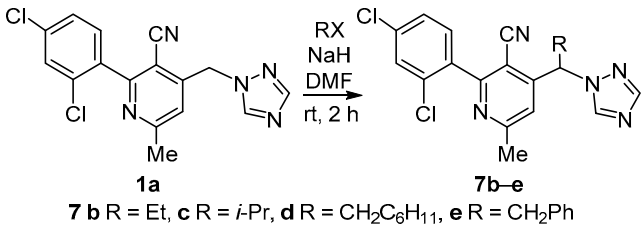



**Table 1**. The reactivity of compounds **1a**–**d** toward MeI

| Entry | Compound | R | Base (1.5 equiv) | Solvent | Product (Yield, %) |
|---|---|---|---|---|---|
| 1 | **1a** | 1-Triazolyl | NaH | DMF | **7a** (75) |
| 2 | **1a** | 1-Triazolyl | NaOH | DMF | **7a** (59) |
| 3 | **1a** | 1-Triazolyl | TEA | DMF | No reaction |
| 4 | **1a** | 1-Triazolyl | $K_2CO_3$ | DMF | No reaction |
| 5 | **1a** | 1-Triazolyl | NaH | THF | **7a** (64) |
| 6 | **1a** | 1-Triazolyl | NaH | DMSO | **7a** (70) |
| 7 | **1a** | 1-Triazolyl | NaH | PhMe | No reaction |
| 8 | **1b** | Methoxy | NaH | DMF | No reaction |
| 9 | **1c** | 1-Pyrrolidinyl | NaH | DMF | No reaction |
| 10 | **1d** | 1-Imidazolyl | NaH | DMF | **8** (70) |

**Table 2**. Reactions of compound **1a** with alkyl halides*

| Entry | RX | Product | Yield, % |
|---|---|---|---|
| 1 | EtI | **7b** | 69 |
| 2 | EtBr | **7b** | 71 |
| 3 | *i*-PrBr | **7c** | 73 |
| 4 | $C_6H_{11}CH_2Br$ | **7d** | 68 |
| 5 | $PhCH_2Br$ | **7e** | 75 |

* Reaction conditions: inert atmosphere ($N_2$), a solution of compound **1a** in DMF was added into a suspension of NaH (1.5 equiv) in DMF at 0°C and stirred for 20 min, RX (2 equiv) was injected into the reaction mixture, and stirring was continued at room temperature.

75% yield (Table 1, entry 1). Other reaction parameters such as the selection of base and solvent were examined. Changing the base to NaOH instead of NaH resulted in a decrease of the yield to 59% (entry 2). No product was observed with TEA or $K_2CO_3$ used as the base (entries 3, 4). When the solvent DMF was replaced with THF, DMSO, or toluene the yield deteriorated or the reaction failed altogether (entries 5–7). The reaction was apparently promoted by polar solvents such as DMF and DMSO.

The reactivity of compound **1a** with other alkyl halides was explored further (Scheme 3), and the results are shown in Table 2. Under the optimal conditions, compound **1a** could react efficiently with a variety of alkyl halides in yields ranging from 68 to 75%. No substantial reactivity difference toward ethyl iodide and ethyl bromide was observed (Table 2, entries 1, 2). It seemed that the steric bulk of these alkylating agents had little effect on the reaction (entries 3, 4). Similar yields were obtained with both isopropyl bromide and cyclohexylmethyl bromide, compared to bromoethane.

In order to further investigate the structure–reactivity relationships of the active methylene group at position 4 of pyridine ring, various functionalities including methoxy, 1-pyrrolidinyl, and 1-imidazolyl groups were also introduced instead of the 1-triazolyl group by mesylation and substitution reactions starting from compound **6** (Scheme 1). The reactions of these derivatives with MeI were carried out under the same conditions (Scheme 2), with the results described in Table 1. As shown in Table 1, the reactivity of the tested compounds was significantly affected by the functional groups connected to the methylene linker. For example, the derivative bearing 1-imidazolyl group could be efficiently methylated with MeI in 70% yield while the substrates containing methoxy or pyrrolidinyl groups failed to undergo this reaction (Table 1, entries 8–9).

The results suggested that the reactivity of carbanions generated from the methylene linker could be effectively enhanced by aromatic nitrogen heterocycles (imidazole and triazole) linked by the methylene group to position 4 of pyridine ring. This might be mainly due to the p-π conjugation between carbanion and two adjacent aromatic conjugated systems, namely, pyridine ring and imidazole or triazole. At the same time, methoxy and pyrrolidinyl groups showed only weak electron-withdrawing effects that were not sufficient to stabilize the carbanion. On the other hand, when the cyano group in compound **1a** was reduced to an aminomethyl group, no hydrogen–deuterium exchange between deuterium oxide and the methylene group adjacent to the aminomethyl group was observed in $^1$H NMR spectra acquired in DMSO-$d_6$ solution. This indicated that the strong electron-withdrawing effects of cyano group might also contribute to delocalization of the negative charge of the carbanion, which would provide an additional stabilizing effect to enhance the reactivity of methylene group toward alkylation reactions.

Thus, we have demonstrated the reactivity of the active methylene group at position 4 of pyridine ring through the reaction of 4-[(triazol-1-yl)methyl]pyridine and 4-[(imidazol-1-yl)methyl]pyridine derivatives with some alkyl halides. The presence of nitrogen heterocycles including imidazole and triazole at the methylene group, as well as the cyano group in the pyridine ring were important for enabling these alkylation reactions, and this method could conveniently provide a series of structurally diverse compounds that may be of interest for medicinal chemists.

## Experimental

$^1$H and $^{13}$C NMR spectra were acquired on a Bruker AV-400 instrument (400 and 100 MHz, respectively) in $CDCl_3$ solution, TMS was used as internal standard. HRMS data were acquired on an Agilent 6210TOF instrument equipped with an electrospray ionization (ESI) source. Melting points were determined on a Buchi Melting Point M-565 apparatus and are uncorrected.

The starting materials were purchased from commercial suppliers and used without further purification. The synthesis of compounds **3** and **4** was performed according to the reported methods.[11,12]

**2-(2,4-Dichlorophenyl)-4-hydroxymethyl-6-methylnicotinonitrile (5)**. A suspension of compound **4** (12.00 g, 35.82 mmol) and $NaBH_4$ (3.40 g, 89.55 mmol) in *t*-BuOH (125 ml) was stirred at 35°C for 6 h. Then the reaction mixture was poured into ice water (200 ml). After cooling the mixture below 5°C, 50% AcOH solution was added to adjust pH to 7. The yellow precipitate was filtered off and purified by recrystallization from EtOAc–petroleum ether mixture to afford 6.83 g (65%) of compound **5** as a light-yellow powder. Yield 65.0%. Mp 148–150°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.56 (1H, t, *J* = 5.2, OH); 2.72 (3H, s, 6-$CH_3$); 4.95 (2H, d, *J* = 5.2, $CH_2$); 7.38 (1H, d, *J* = 8.4, H-6 Ar); 7.41 (1H, dd, *J* = 8.4, *J* = 2.0, H-5 Ar); 7.55 (1H, d, *J* = 2.0, H-3 Ar); 7.57 (1H, s, H-5 Py). $^{13}$C NMR spectrum, δ, ppm: 25.1; 61.7; 105.0; 114.7; 120.1; 127.5; 130.0; 131.5; 133.6; 135.3; 136.3; 154.3; 159.0; 162.9. Found, *m*/*z*: 292.0177 $[M]^+$. $C_{14}H_{10}Cl_2N_2O$. Calculated, *m*/*z*: 292.0170.

**2-(2,4-Dichlorophenyl)-6-methyl-4-[(1*H*-1,2,4-triazol-1-yl)methyl]nicotinonitrile (1a)**. DEAD (1.67 g, 9.57 mmol) was added to a solution of compound **5** (2.00 g, 6.83 mmol), 1,2,4-triazole (0.66 g, 9.57 mmol), and $Ph_3P$ (2.51 g, 9.57 mmol) in THF (20 ml) at 0–5°C. The mixture was stirred at ambient temperature for 2 h and the solvent was evaporated under vacuum. The residue was dissolved in $CH_2Cl_2$ (35 ml) and 3 N HCl/MeOH solution (4 ml) was added to form the hydrochloride salt which was separated by filtration. Then the filtrate was added to a mixture of $H_2O$ (10 ml) and $CH_2Cl_2$ (10 ml), and 2 N NaOH solution was added to basify the aqueous layer, followed by extraction with $CH_2Cl_2$ (5×10 ml). The organic layers were combined, dried over $Na_2SO_4$, and evaporated under reduced pressure to give 2.1 g (83%) of compound **1a** as a light-yellow solid. Mp 125–127°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.65 (3H, s, 6-$CH_3$); 5.60 (2H, s, $CH_2$); 7.00 (1H, s, H-5 Py); 7.36 (1H, d, *J* = 8.4, H-6 Ar); 7.40 (1H, dd, *J* = 8.4, *J* = 1.6, H-5 Ar); 7.55 (1H, d, *J* = 1.6, H-3 Ar); 8.06 (1H, s, H triazole); 8.31 (1H, s, H triazole). $^{13}$C NMR spectrum, δ, ppm: 25.2; 50.5; 106.2; 114.6; 121.3; 127.6; 130.1; 131.6; 133.5; 134.9; 136.6; 144.3; 147.7; 153.2; 159.7; 163.7. Found, *m*/*z*: 343.0394 $[M]^+$. $C_{16}H_{11}Cl_2N_5$. Calculated, *m*/*z*: 343.0392.

**[3-Cyano-2-(2,4-dichlorophenyl)-6-methylpyridin-4-yl]-methyl methanesulfonate (6)**. MsCl (0.234 g, 2.05 mmol) was added to a solution of compound **5** (0.500 g, 1.71 mmol) and TEA (0.380 g, 3.42 mmol) in THF (5 ml) at 0–5°C. The mixture was stirred at ambient temperature for 2 h. Then $H_2O$ (5 ml) was added and the aqueous phase was extracted with EtOAc (2×5 ml). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using $CH_2Cl_2$ as eluent to give 0.521 g (83%) of compound **6**. Mp 86–87°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.75 (3H, s, 6-$CH_3$); 3.21 (3H, s, $SO_2CH_3$); 5.45 (2H, s, $CH_2$); 7.41 (2H, m, H-5,6 Ar); 7.50 (1H, s, H-3 Ar); 7.58 (1H, s, H-5 Py). $^{13}$C NMR spectrum, δ, ppm: 25.2; 38.0; 66.8; 105.8; 114.4; 121.2; 127.6; 130.0; 131.6; 133.6; 135.0; 136.6; 146.7; 159.5; 163.6. Found, *m*/*z*: 369.9953 $[M]^+$. $C_{15}H_{12}Cl_2N_2O_3S$. Calculated, *m*/*z*: 369.9946.

**2-(2,4-Dichlorophenyl)-4-(methoxymethyl)-6-methylnicotinonitrile (1b)**. A mixture of compound **6** (0.260 g, 0.70 mmol) and MeONa (0.076 g, 1.41 mmol) in MeOH (5 ml) was stirred at room temperature for 18 h. Then $H_2O$ (5 ml) was added and the solution was adjusted to pH 7 with 2 N HCl solution. The aqueous phase was extracted with EtOAc (3×5 ml). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using $CH_2Cl_2$ as eluent to give 0.179 g (83%) of product **1b**. Mp 95–96°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.71 (3H, s, 6-$CH_3$); 3.57 (3H, s, $CH_3$); 4.71 (2H, s, $CH_2$); 7.38 (1H, d, *J* = 8.0, H-6 Ar); 7.41 (1H, d, *J* = 8.0, *J* = 1.6, H-5 Ar); 7.50 (1H, s, H-5 Py); 7.56 (1H, d, *J* = 1.6, H-3 Ar). $^{13}$C NMR spectrum, δ, ppm: 25.2; 59.3; 71.1; 105.4; 114.8; 120.4; 127.5; 129.9; 131.6; 133.7; 135.5; 136.2; 151.9; 159.0; 162.8. Found, *m*/*z*: 306.0327 $[M]^+$. $C_{15}H_{12}Cl_2N_2O$. Calculated, *m*/*z*: 306.0327.

**Synthesis of nicotinonitriles 1c,d** (General method). A mixture of compound **6** (1.50 g, 4.05 mmol), pyrrolidine or imidazole (8.11 mmol), and $K_2CO_3$ (0.67 g, 4.86 mmol) in MeCN (15 ml) was stirred at room temperature for 5 h. After the reaction was complete, the solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography using 60:1 $CH_2Cl_2$–MeOH as eluent, giving the pure products **1c**,**d**.

**2-(2,4-Dichlorophenyl)-6-methyl-4-(pyrrolidin-1-ylmethyl)nicotinonitrile (1c)**. Yield 73%. White solid. Mp 103–104°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.86–1.89 (4H, m, H pyrrolidine); 2.65–2.67 (4H, m, H pyrrolidine); 2.70 (3H, s, 6-$CH_3$); 3.91 (2H, s, $CH_2$); 7.40 (2H, s, H-5,6 Ar); 7.51 (1H, s, H-5 Py); 7.56 (1H, s, H-3 Ar). $^{13}$C NMR spectrum, δ, ppm: 23.7 (2C); 25.0 (2C); 54.3; 57.5; 107.2; 115.3; 122.4; 127.4; 129.9; 131.6; 133.7; 135.7; 136.1; 153.3; 159.1; 162.3. Found, *m*/*z*: 345.0793 $[M]^+$. $C_{18}H_{17}Cl_2N_3$. Calculated, *m*/*z*: 345.0800.

**2-(2,4-Dichlorophenyl)-4-[(1*H*-imidazol-1-yl)methyl]-6-methylnicotinonitrile (1d)**. Yield 81%. Light-yellow solid. Mp 110–112°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.64 (3H, s, 6-$CH_3$); 5.42 (2H, s, $CH_2$); 6.72 (1H, s, H-5 Py); 7.04 (1H, s, H imidazole); 7.24 (1H, s, H imidazole); 7.39 (1H, d, *J* = 8.0, H-6 Ar); 7.44 (1H, dd, *J* = 8.0, *J* = 1.6, H-5 Ar); 7.59 (1H, d, *J* = 1.6, H-3 Ar); 7.67 (1H, s, H imidazole). $^{13}$C NMR spectrum, δ, ppm: 25.2; 48.0; 105.7; 114.6; 119.5; 120.0; 127.6; 130.0; 130.9; 131.5; 133.5; 135.0;

136.6; 137.8; 149.7; 159.6; 163.9. Found, *m/z*: 342.0435 $[M]^+$. $C_{17}H_{12}Cl_2N_4$. Calculated, *m/z*: 342.0439.

**Synthesis of nicotinonitriles 7a–e** (General method). A solution of compound **1a** (1.00 g, 2.91 mmol) in DMF (2 ml) was added under $N_2$ atmosphere to a cooled (0°C) suspension of NaH (0.17 g, 4.36 mmol) in anhydrous DMF (8 ml). After 20 min of stirring, the appropriate alkyl halide (5.82 mmol) was injected. The mixture was stirred at room temperature for 2 h. After the reaction was complete, saturated $NH_4Cl$ solution (50 ml) was added and the water phase was extracted with EtOAc (3×15 ml). The organic phase was collected, dried over $Na_2SO_4$, and evaporated under vacuum. The residue was purified by silica gel column chromatography using $CH_2Cl_2$–MeOH, 50:1 as eluent, giving the pure products **7a**–**e**.

**2-(2,4-Dichlorophenyl)-6-methyl-4-[1-(1*H*-1,2,4-triazol-1-yl)ethyl]nicotinonitrile (7a)**. Yield 75%. White solid. Mp 110–111°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.06 (3H, d, *J* = 6.8, CHC$\underline{H}_3$); 2.66 (3H, s, 6-$CH_3$); 5.98 (1H, q, *J* = 6.8, C$\underline{H}$CH$_3$); 7.13 (1H, s, H-5 Py); 7.39 (1H, d, *J* = 8.4, H-6 Ar); 7.43 (1H, d, *J* = 8.4, H-5 Ar); 7.58 (1H, s, H-3 Ar); 8.08 (1H, s, H triazole); 8.34 (1H, s, H triazole). $^{13}$C NMR spectrum, δ, ppm: 20.5; 25.3; 56.7; 106.7; 114.7; 119.5; 127.6; 130.0; 131.6; 133.6; 135.1; 136.6; 143.0; 152.8; 153.1; 159.7; 163.7. Found, *m/z*: 357.0552 $[M]^+$. $C_{17}H_{13}Cl_2N_5$. Calculated, *m/z*: 357.0548.

**2-(2,4-Dichlorophenyl)-6-methyl-4-[1-(1*H*-1,2,4-triazol-1-yl)propyl]nicotinonitrile (7b)**. Yield 71%. White solid. Mp 105–106°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.01 (3H, t, *J* = 7.2, CHCH$_2$C$\underline{H}_3$); 2.26–2.33 (1H, m) and 2.55–2.59 (1H, m, CHC$\underline{H}_2$CH$_3$); 2.68 (3H, s, 6-$CH_3$); 5.64–5.68 (1H, m, C$\underline{H}$CH$_2$CH$_3$); 7.39 (1H, d, *J* = 8.4, H-6 Ar); 7.42 (1H, dd, *J* = 8.4, *J* = 1.6, H-5 Ar); 7.44 (1H, s, H-5 Py); 7.58 (1H, d, *J* = 1.6, H-3 Ar); 8.10 (1H, s, H triazole); 8.35 (1H, s, H triazole). $^{13}$C NMR spectrum, δ, ppm: 10.9; 25.3; 28.3; 62.6; 106.3; 114.9; 120.2; 127.6; 130.0; 131.6; 133.6; 135.2; 136.5; 143.9; 151.9; 152.9; 159.5; 163.6. Found, *m/z*: 371.0701 $[M]^+$. $C_{18}H_{15}Cl_2N_5$. Calculated, *m/z*: 371.0705.

**2-(2,4-Dichlorophenyl)-6-methyl-4-[2-methyl-1-(1*H*-1,2,4-triazol-1-yl)propyl]nicotinonitrile (7c)**. Yield 73%. White solid. Mp 136–138°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.93 (3H, d, *J* = 6.8) and 1.00 (3H, d, *J* = 6.8, CHCH(C$\underline{H}_3$)$_2$); 2.72 (3H, s, 6-$CH_3$); 2.83–2.92 (1H, m, CHC$\underline{H}$(CH$_3$)$_2$); 5.32 (1H, d, *J* = 10.4, C$\underline{H}$CH(CH$_3$)$_2$); 7.39 (1H, d, *J* = 8.4, H-6 Ar); 7.43 (1H, dd, *J* = 8.4, *J* = 2.0, H-5 Ar); 7.58 (1H, d, *J* = 2.0, H-3 Ar); 7.84 (1H, s, H-5 Py); 8.07 (1H, s, H triazole); 8.26 (1H, s, H triazole). $^{13}$C NMR spectrum, δ, ppm: 19.0; 19.6; 25.4; 33.5; 67.1; 107.4; 115.3; 121.1; 127.6; 130.0; 131.5; 133.6; 135.3; 136.5; 144.1; 150.7; 153.0; 159.3; 163.4. Found, *m/z*: 385.0859 $[M]^+$. $C_{19}H_{17}Cl_2N_5$. Calculated, *m/z*: 385.0861.

**2-(2,4-Dichlorophenyl)-4-[2-cyclohexyl-1-(1*H*-1,2,4-triazol-1-yl)ethyl]-6-methylnicotinonitrile (7d)**. Yield 68%. White solid. Mp 75–76°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.05–1.19 (6H, m, H cyclohexyl); 1.66–1.74 (4H, m, H cyclohexyl); 1.88 (1H, s, H cyclohexyl); 1.96–2.03 (1H, m) and 2.48–2.52 (1H, m, CHC$\underline{H}_2$); 2.67 (3H, s, 6-$CH_3$); 5.90–5.93 (1H, m, C$\underline{H}$CH$_2$); 7.39 (1H, s, H-5 Py); 7.39 (1H, d, *J* = 8.4, H-6 Ar); 7.43 (1H, dd, *J* = 8.4, *J* = 2.0, H-5 Ar); 7.57 (1H, d, *J* = 2.0, H-3 Ar); 8.10 (1H, s, H triazole); 8.30 (1H, s, H triazole). $^{13}$C NMR spectrum, δ, ppm: 25.3; 25.8; 26.0; 26.1; 32.1; 33.4; 34.2; 42.3; 58.6; 106.0; 114.8; 120.1; 127.6; 130.0; 131.6; 133.6; 135.2; 136.5; 143.8; 152.5; 152.8; 159.5; 163.5. Found, *m/z*: 439.1333 $[M]^+$. $C_{23}H_{23}Cl_2N_5$. Calculated, *m/z*: 439.1331.

**2-(2,4-Dichlorophenyl)-6-methyl-4-[2-phenyl-1-(1*H*-1,2,4-triazol-1-yl)ethyl]nicotinonitrile (7e)**. Yield 75%. Light-yellow oil. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.73 (3H, s, 6-$CH_3$); 3.45–3.50 (1H, m) and 3.77–3.83 (1H, m, CHC$\underline{H}_2$); 5.89–5.93 (1H, m, C$\underline{H}$CH$_2$); 7.08–7.10 (2H, m, H Ph); 7.25–7.26 (3H, m, H Ph); 7.37 (1H, d, *J* = 8.0, H-6 Ar); 7.42 (1H, dd, *J* = 8.0, *J* = 1.6, H-5 Ar); 7.57 (1H, d, *J* = 1.6, H-3 Ar); 7.71 (1H, s, H-5); 8.03 (1H, s, H triazole); 8.11 (1H, s, H triazole). $^{13}$C NMR spectrum, δ, ppm: 25.4; 41.3; 62.9; 106.3; 114.9; 120.5; 127.6; 127.7; 128.9; 129.0; 130.0; 131.6; 133.6; 135.1 (2C); 136.6; 144.3; 151.2; 152.8; 159.5; 163.6. Found, *m/z*: 433.0858 $[M]^+$. $C_{23}H_{17}Cl_2N_5$. Calculated, *m/z*: 433.0861.

**2-(2,4-Dichlorophenyl)-4-[1-(1*H*-imidazol-1-yl)ethyl]-6-methylnicotinonitrile (8)**. A solution of compound **1d** (1.00 g, 2.91 mmol) in DMF (2 ml) was added under $N_2$ atmosphere to a cooled (0°C) suspension of NaH (0.17 g, 4.36 mmol) in anhydrous DMF (8 ml). After stirring for 20 min, MeI (0.83g, 5.82 mmol) was injected. The mixture was stirred at room temperature for additional 2 h. After the reaction was complete, saturated $NH_4Cl$ solution (50 ml) was added and the water phase was extracted with EtOAc (3×15 ml). The organic phase was collected, dried over $Na_2SO_4$, and evaporated under vacuum. The residue was purified by silica gel column chromatography using $CH_2Cl_2$–MeOH, 40:1, as eluent, giving 0.73 g (70%) of product **8**. Yellow solid. Mp 102–104°C. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.01 (3H, d, *J* = 6.8, CHC$\underline{H}_3$); 2.63 (3H, s, 6-$CH_3$); 5.75–5.80 (1H, m, C$\underline{H}$CH$_3$); 6.76 (1H, s, H-5 Py); 7.07 (1H, s, H imidazole); 7.22 (1H, s, H imidazole); 7.40 (1H, d, *J* = 8.4, H-6 Ar); 7.44 (1H, dd, *J* = 8.4, *J* = 2.0, H-5 Ar); 7.59 (1H, d, *J* = 2.0, H-3 Ar); 7.74 (1H, s, H imidazole). $^{13}$C NMR spectrum, δ, ppm: 20.8; 25.3; 54.4; 105.5; 114.7; 118.2; 118.5; 127.6; 130.0; 130.3; 131.5; 133.6; 135.1; 136.1; 136.6; 155.0; 159.8; 163.9. Found, *m/z*: 356.0600 $[M]^+$. $C_{18}H_{14}Cl_2N_4$. Calculated, *m/z*: 356.0596.

A Supplementary information file containing the procedures for synthesis of compounds **3** and **4**, $^1$H and $^{13}$C NMR spectra of the synthesized compounds is available at http://link.springer.com/journal/10593.

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