(Cyanomethyl)trialkylphosphonium Iodides: Efficient Reagents for the Intermolecular Alkylation of Amines with Alcohols in Solution and on Solid Phase

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One of the most frequently used procedures for the preparation of tertiary amines is *N*-alkylation of secondary amines by treatment with alkylating agents (alkyl halides, sulfonates, oxiranes, etc.) or reductive alkylation with aldehydes or ketones. Few alkylating agents with interesting pharmacophoric groups are, however, commercially available, and many of them are toxic. Aldehydes are often unstable and cannot be stored for a long time.

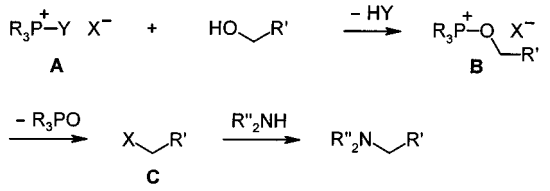
For our parallel synthesis program, we have been seeking a reagent which would mediate the direct alkylation of amines with alcohols.[1] Alcohols are usually stable and easy to handle, can be purchased with a broad variety of additional functional groups, and are therefore ideal building blocks for the production of compound libraries.[2] Phosphonium salts **A** (Scheme 1) appeared to be promising candidates for such a reaction, which could proceed as outlined in Scheme 1. Due to the strength of phosphorus−oxygen bonds, a phosphonium salt **A** should selectively react with alcohols, even in the presence of secondary amines. Because alkoxyphosphonium salts such as **B** react faster with anionic nucleophiles than with neutral nucleophiles, and generally do not react smoothly with amines,[1] salts **B** are not expected to react with the amine, but to be converted into **C**. Anion X^- must be a suitable leaving group, so that intermediate **C** is sufficiently reactive to alkylate the amine.

The phosphonium salt $[Ph_3P^+-N(Me)Ph][I^-]$[3] as well as the phosphorane $Ph_3P(OCH_2CF_3)_2$ [4] has been used previously to alkylate amines with alcohols, but these reagents are highly water-sensitive and lead to the formation of various byproducts (Ph_3PO, PhNHMe) which are difficult to separate from the desired tertiary amines. Our aim was to find a reagent useful for parallel synthesis, which should be stable, easy to handle, and yield crude products of high purity.

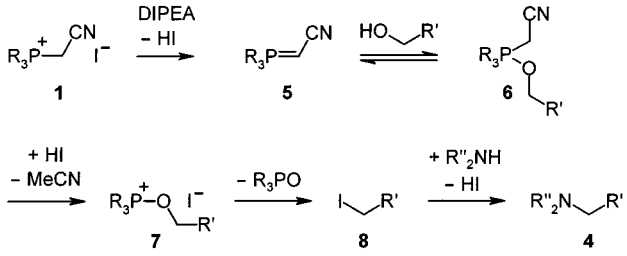
Results and Discussion

We found that (cyanomethyl)trialkylphosphonium iodides **1** (Scheme 2[5]) cleanly underwent the reaction

Scheme 1. Proposed Mechanism for a Phosphonium Salt Mediated Alkylation of Amines with Alcohols.



Scheme 2. Proposed Mechanism for the Alkylation of Amines by Alcohols with the Aid of (Cyanomethyl)phosphonium Iodides 1.



sketched in Scheme 1. Illustrative examples are listed in Table 1. The reaction required heating and the presence of a tertiary amine to proceed to completion.[6] Analysis of the crude products by ^{1}H NMR and HPLC only revealed the presence of starting materials and the desired product, and we assume that the fair yields were due to losses during recrystallization. Secondary alcohols could not be used in this reaction. Other suitable solvents for this reaction, in addition to propionitrile, were acetonitrile and dioxane, but in propionitrile at 90 °C the reaction was homogeneous in all the cases studied and proceeded faster than in dioxane (at 90 °C) or than in refluxing acetonitrile (81 °C). For alkylations in solution, the trimethylphosphonium iodide **1a** (Table 1) proved particularly advantageous, because the byproduct formed (Me_3PO) is water-soluble and can be easily separated from the products. For reactions on solid phase (polystyrene cross-linked with 1% divinylbenzene), on the other hand, both **1a** and **1b** were equally suitable. Support-bound amines (**3i** and **3j**, Table 1) underwent the reaction cleanly, and no quaternization of the amines was observed.[7]

A proposed mechanism for this new reaction is shown in Scheme 2. It has been reported[8] that some stabilized phosphorus ylides react with alcohols to yield symmetric

(1) Zaragoza, F.; Stephensen, H. *Tetrahedron Lett.* **2000**, *41*, 1841−1844.

(2) (a) Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000. (b) Zaragoza, F.; Stephensen, H. *Angew. Chem.* **2000**, *112*, 565−567; *Angew. Chem., Int. Ed.* **2000**, *39*, 554−556.

(3) Tanigawa, Y.; Murahashi, S.; Moritani, I. *Tetrahedron Lett.* **1975**, 471−472. Several attempts by us to use $[Ph_3P^+-N(Me)Ph][I^-]$ for the alkylation of resin-bound amines with alcohols were unsuccessful.

(4) Kubota, T.; Miyashita, S.; Kitazume, T.; Ishikawa, N. *J. Org. Chem.* **1980**, *45*, 5052−5057. Phosphoranes $R_3P(OCH_2CF_3)_2$ are so unstable and sensitive to moisture that Kubota et al. were unable to isolate them.

(5) We also prepared the corresponding (cyanomethyl)phosphonium triflates, which showed a better solubility but a similar reactivity as the iodides.

(6) Kinetic studies, performed by treating an equimolar mixture of 1-(3-chlorophenyl)piperazine and 3-phenyl-1-propanol (each 0.5 mol L^{-1} in propionitrile) with **1a** (1.2 equiv) and DIPEA (1.3 equiv) at various temperatures and following the progress of the reaction by HPLC-MS, showed that the reaction at 40 °C proceeded with a half-life of 1.25 h and required at least 22 h to attain >98% conversion.

(7) The quaternization of amines on cross-linked polystyrene only proceeds smoothly with strong alkylating agents (benzylic or allylic halides) and generally requires higher temperatures and longer reaction times than those used in the current procedure. In solution, however, quaternization was observed when an excess of alcohol and phosphonium salt was used.

(8) (a) Grayson, M.; Keough, P. T. *J. Am. Chem. Soc.* **1960**, *82*, 3919−3924. (b) Pappas, J. J.; Gancher, E. *J. Org. Chem.* **1966**, *31*, 1287−1289.

10.1021/jo001735p CCC: $20.00
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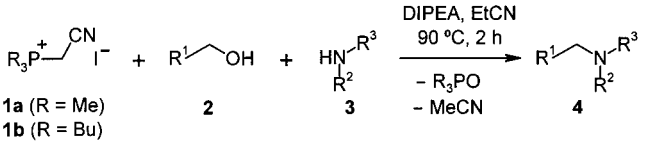
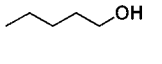
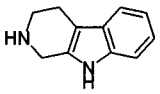
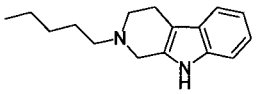
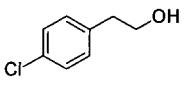
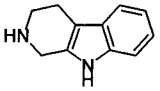
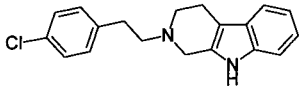
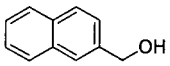
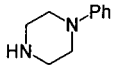
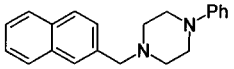
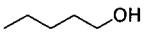
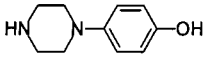
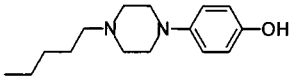
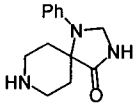
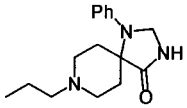
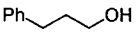
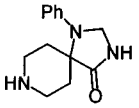
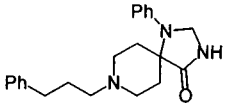
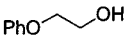
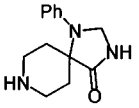
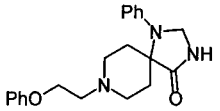
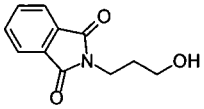
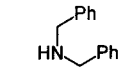
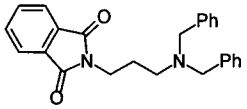
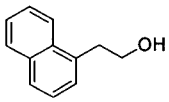
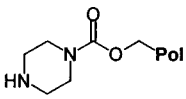
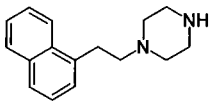
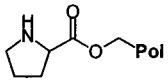
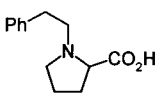
Table 1. Phosphonium Iodide Mediated Alkylation of Secondary Amines by Alcohols[a]



Entry	Alcohol 2	Amine 3[b]	Product 4	Yield[c]
a				74%
b				83%
c				70%
d				76%
e				74%
f				80%
g				73%
h				68%
i				83%[d]
j				76%[d]

[a] Entries **a**−**h**: phosphonium salt **1a** (1.2 equiv) and diisopropylethylamine (DIPEA, 1.3 equiv) were added to an equimolar mixture of the alcohol and the amine (both 1.0 equiv, 0.50 mol L^{-1}) in propionitrile. The mixture was stirred at 90 °C for 2 h. Entries **i**, **j**: the resin-bound amines **3** (1.0 equiv) were treated with a solution of the alcohol **2** (7.2 equiv, 0.56 mol L^{-1}), salt **1b** (6.1 equiv), and DIPEA (8.1 equiv) in acetonitrile at 80 °C for 15 h. [b] **Pol**: 1% cross-linked polystyrene with Wang linker. [c] Yields of recrystallized products. [d] Yield of trifluoroacetate salt after cleavage from the support.

ethers, presumably via alkoxyphosphonium alkoxides such as **B** (Scheme 1, $X^- = RO^-$). (Cyanomethyl)-phosphonium salts (pK_{HA} 7[9]) can be deprotonated by diisopropylethylamine (DIPEA) and can then react with alcohols to yield intermediates **6**.[10] Thermolysis of the latter in the presence of DIPEA hydroiodide leads to P−C bond cleavage and release of acetonitrile, to yield alkoxyphosphonium iodides **7**, which are known to decompose smoothly to yield alkyl iodides **8**.[11] These react with amines, to yield tertiary amines **4** or quaternary ammonium salts, if an excess of alcohol and phosphonium iodide is used.

We conclude that reagents **1** efficiently promote the direct, intermolecular *N*-alkylation of amines with alcohols. Phosphonium iodides **1** are easy to prepare and to handle and do not react with air, water, or alcohols at

(9) Zhang, X.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968−972.

(10) The isolated (cyanomethylene)phosphoranes **5** have been used with success for Mitsunobu-type chemistry: Itô, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, *71*, 1053−1057. Isolated (cyanomethylene)phosphoranes **5** do not mediate the intermolecular *N*-alkylation of amines with alcohols, because alkoxyphosphonium salts **7** can, in the absence of other anions, only be formed as alkoxide salts in this case, which mainly decompose to yield ethers. The intermolecular *N*-alkylation of ammonium iodides under conditions of the Mitsunobu reaction has recently been reported by us.[1]

(11) Rydon, H. N. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. VI, pp 830−832. The proposed mechanism is substantiated further by our observation, that under similar reaction conditions as described herein, (cyanomethyl)tributylphosphonium chloride cleanly converts primary aliphatic alcohols into the corresponding chlorides.

room temperature. We found these reagents to offer a convenient alternative to synthetic protocols, in which an alcohol first is converted into an alkylating agent, which is then used to alkylate an amine in a second step. Currently we are exploring the scope of nucleophiles which can be alkylated with these reagents and will report our results in due course.

Experimental Section

(Cyanomethyl)trimethylphosphonium Iodide (1a). A solution of trimethylphosphine in toluene (1 mol L^{-1}, 80 mL, 80 mmol) at 0 °C under nitrogen was diluted with toluene (40 mL) and tetrahydrofuran (40 mL). Iodoacetonitrile (5.60 mL, 77.5 mmol) was then added dropwise while stirring energetically, whereby a colorless solid precipitated. When the addition was finished, the ice-bath was removed and stirring was continued at room temperature for 40 h. The mixture was filtered, and the solid was washed with toluene and dried under reduced pressure. Recrystallization from acetonitrile (50 mL) yielded 14.7 g (78%) of the title compound as colorless crystals: mp 258−259 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.07 (d, J = 17 Hz, 9H), 4.06 (d, J = 17 Hz, 2H). Anal. Calcd for $C_5H_{11}INP$ (243.03): C, 24.71; H, 4.56; N, 5.76. Found: C, 24.81; H, 4.60; N, 5.68.

Note: If an excess of iodoacetonitrile is used, a colored product in lower yield may be obtained after recrystallization.

(Cyanomethyl)tributylphosphonium Iodide (1b). To a solution of tributylphosphine (85.7 g, 424 mmol) in toluene (275 mL) at 0 °C under nitrogen was added iodoacetonitrile (71.4 g, 428 mmol) at such a rate that the temperature remained <12 °C, while stirring energically. The mixture was kept at room temperature for 18 h and was filtered, and the solid was dried under reduced pressure. This solid was dissolved in hot acetonitrile (75 mL), and then ethyl acetate (1.0 L) was added while stirring at 78 °C. The mixture was kept at room-temperature overnight, whereby the product crystallized. Filtration and drying under reduced pressure yielded 139 g (89%) of the title compound as colorless needles, mp 105−106 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (t, J = 7 Hz, 9H), 1.43 (sext, J = 7 Hz, 6H), 1.50−1.61 (m, 6H), 2.38−2.46 (m, 6H), 4.21 (br d, J = 17 Hz, 2H). Anal. Calcd for $C_{14}H_{29}INP$ (369.27): C, 45.54; H, 7.92; N, 3.79. Found: C, 45.73; H, 8.02; N, 3.76.

General Procedure for the Alkylation of Amines with Alcohols. 8-(2-Phenoxyethyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (4g). The phosphonium iodide **1a** (590 mg, 2.43 mmol) was added to a mixture of 2-phenoxyethanol (294 mg, 2.13 mmol; **2g**), 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (468 mg, 2.02 mmol; **3g**), DIPEA (0.46 mL, 2.63 mmol), and propionitrile (4.0 mL), and the mixture was stirred at 90 °C for 2 h. The mixture was allowed to cool to room temperature, whereby it solidified. A solution of potassium carbonate (2.1 g) in water (30 mL) was added, and the product was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (2 × 20 mL), dried with magnesium sulfate, and concentrated under reduced pressure, to yield 747 mg of a solid. Recrystallization from ethanol yielded 517 mg (73%) of the title compound as colorless, microcrystalline solid: mp 219−222 °C; HPLC-MS m/z 352 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.57 (br d, J = 14 Hz, 2H), 2.50−2.60 (m, 2H), 2.75 (t, J = 6 Hz, 2H), 2.83 (m, 4H), 4.10 (t, J = 6 Hz, 2H), 4.57 (s, 2H), 6.75 (t, J = 7 Hz, 1H), 6.84 (d, J = 8 Hz, 2H), 6.90−6.99 (m, 3H), 7.20−7.31 (m, 4H), 8.64 (s, 1H). Anal. Calcd for $C_{21}H_{25}N_3O_2$ (351.45): C, 71.77; H, 7.17; N, 11.96. Found: C, 71.49; H, 7.36; N, 11.87.

With the same procedure as used for the preparation of **4g**, the following compounds were prepared:

2-Pentyl-2,3,4,9-tetrahydro-1*H*-β-carboline (4a). Yield: 74%; mp 119−120 °C (MeCN); HPLC-MS m/z 243 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 (t, J = 7 Hz, 3H), 1.31 (m, 4H), 1.53 (m, 2H), 2.49−2.53 (m, 2H), 2.66 (m, 2H), 2.73 (m, 2H), 3.56 (br s, 2H), 6.93 (t, J = 7 Hz, 1H), 6.99 (t, J = 7 Hz, 1H), 7.26 (d, J = 7 Hz, 1H), 7.34 (d, J = 7 Hz, 1H), 10.65 (s, 1H). Anal. Calcd for $C_{16}H_{22}N_2$ (242.37): C, 79.29; H, 9.15; N, 11.56. Found: C, 79.21; H, 9.19; N, 11.35.

2-(4-Chlorophenethyl)-2,3,4,9-tetrahydro-1*H*-β-carboline (4b). Yield: 83%; mp 193−195 °C (MeCN); HPLC-MS m/z 311 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.65−2.73 (m, 2H), 2.75−2.89 (m, 6H), 3.65 (s, 2H), 6.93 (t, J = 7 Hz, 1H), 7.00 (t, J = 7 Hz, 1H), 7.22−7.35 (m, 6H), 10.68 (s, 1H). Anal. Calcd for $C_{19}H_{19}ClN_2$ (310.83): C, 73.42; H, 6.16; N, 9.01. Found: C, 73.43; H, 6.37; N, 8.97.

1-(2-Naphthylmethyl)-4-phenylpiperazine (4c). Yield: 70%; mp 158−159 °C (MeCN); HPLC-MS m/z 303 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.55 (m, 4H), 3.14 (m, 4H), 3.68 (s, 2H), 6.76 (t, J = 8 Hz, 1H), 6.91 (d, J = 8 Hz, 2H), 7.19 (t, J = 8 Hz, 2H), 7.46−7.55 (m, 3H), 7.82 (s, 1H), 7.90 (m, 3H). Anal. Calcd for $C_{21}H_{22}N_2$ (302.42): C, 83.40; H, 7.33; N, 9.26. Found: C, 83.36; H, 7.48; N, 9.26.

4-(4-Pentylpiperazino)phenol (4d). Yield: 76%; mp 175−177 °C (aqueous EtOH); HPLC-MS m/z 249 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (t, J = 7 Hz, 3H), 1.22−1.35 (m, 4H), 1.44 (quint, J = 7 Hz, 2H), 2.28 (t, J = 7 Hz, 2H), 2.46 (m, 4H), 2.93 (br s, 4H), 6.63 (d, J = 8 Hz, 2H), 6.76 (d, J = 8 Hz, 2H), 8.79 (s, 1H). Anal. Calcd for $C_{15}H_{24}N_2O$ (248.37): C, 72.54; H, 9.74; N, 11.28. Found: C, 72.34; H, 10.15; N, 11.27.

1-Phenyl-8-propyl-1,3,8-triazaspiro[4.5]decan-4-one (4e). Yield: 74%; mp 206−207 °C (AcOEt); HPLC-MS m/z 274 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 (t, J = 7 Hz, 3H), 1.47 (q, J = 7 Hz, 2H), 1.58 (br d, J = 14 Hz, 2H), 2.30 (m, 2H), 2.50−2.58 (m, 2H), 2.62−2.80 (m, 4H), 4.56 (s, 2H), 6.73 (t, J = 7 Hz, 1H), 6.84 (m, 2H), 7.22 (m, 2H), 8.61 (s, 1H). Anal. Calcd for $C_{16}H_{23}N_3O$ (273.38): C, 70.30; H, 8.48; N, 15.37. Found: C, 70.33; H, 8.64; N, 15.38.

1-Phenyl-8-(3-phenylpropyl)-1,3,8-triazaspiro[4.5]decan-4-one (4f). Yield: 80%; mp 172−173 °C (MeCN); HPLC-MS m/z 350 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.55 (br d, J = 14 Hz, 2H), 1.75 (quint, J = 7 Hz, 2H), 2.33 (t, J = 7 Hz, 2H), 2.46−2.78 (m, 8H), 4.57 (s, 2H), 6.74 (m, 1H), 6.85 (m, 2H), 7.12−7.30 (m, 7H), 8.62 (s, 1H). Anal. Calcd for $C_{22}H_{27}N_3O$ (349.48): C, 75.61; H, 7.79; N, 12.02. Found: C, 75.30; H, 8.04; N, 12.16.

***N*-[3-(Dibenzylamino)propyl]phthalimide (4h).** Yield: 68%; mp 113−115 °C (EtOH); HPLC-MS m/z 385 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (m, 2H), 2.38 (m, 2H), 3.46−3.57 (m, 6H), 7.13−7.39 (m, 10H), 7.83 (br s, 4H). Anal. Calcd for $C_{25}H_{24}N_2O_2$ (384.48): C, 78.10; H, 6.29; N, 7.29. Found: C, 77.99; H, 6.57; N, 7.21.

1-[2-(1-Naphthyl)ethyl]piperazine Trifluoroacetate (4i). To Wang-resin-bound piperazine[12] (1.05 g, 0.71 mmol) were added phosphonium iodide **1b** (1.85 g, 5.01 mmol) and a solution of 2-(1-naphthyl)ethanol (1.04 g, 6.04 mmol) and DIPEA (1.25 mL, 7.16 mmol) in acetonitrile (15 mL). The mixture was shaken at 80 °C for 15 h and filtered, and the resin was washed extensively with *N*-methylpyrrolidinone (NMP), dichloromethane, and methanol. Dichloromethane (5 mL) and trifluoroacetic acid (5 mL) were added, and the mixture was shaken at 20 °C for 45 min. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was redissolved in ethyl acetate (4 mL), and upon addition of heptane the title compound precipitated. A colorless solid (278 mg, 83%) was obtained: mp 191−193 °C; HPLC-MS m/z 241 [MH$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.20−3.55 (m, 12H), 7.45−7.51 (m, 2H), 7.57 (m, 2H), 7.87 (m, 1H), 7.96 (m, 1H), 8.13 (m, 1H), 9.35 (br s, 3H). Anal. Calcd for $C_{20}H_{22}F_6N_2O_4$ (468.40): C, 51.29; H, 4.73; N, 5.98. Found: C, 51.47; H, 4.77; N, 5.93.

***N*-(Phenethyl)proline Trifluoroacetate (4j).** To Wang-resin-bound *N*-Fmoc proline (0.73 g, 0.55 mmol) were added NMP (8.0 mL) and piperidine (2.0 mL), and the mixture was shaken at room temperature for 25 min. The resin was filtered and washed with NMP. To the support were added phosphonium iodide **1b** (1.23 g, 3.33 mmol) and a solution of 2-phenylethanol (0.47 mL, 3.92 mmol) and DIPEA (0.77 mL, 4.41 mmol) in acetonitrile (7.0 mL). The mixture was shaken at 81 °C for 23 h and filtered, and the resin was washed extensively with NMP, dichloromethane, and methanol. Dichloromethane (4.0 mL) and trifluoroacetic acid (4.0 mL) were added, and the mixture was shaken at 20 °C for 35 min. Filtration and concentration of the filtrate yielded an oil, which was redissolved in methanol (1 mL).

(12) Zaragoza, F.; Petersen, S. V. *Tetrahedron* **1996**, *52*, 10823−10826.

The product crystallized upon addition of diethyl ether. The title compound (115 mg, 76%) was obtained as light-brown needles, mp 176−178 °C. HPLC-MS *m*/*z* 220 [MH^+]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.87 (m, 1H), 1.94−2.06 (m, 2H), 2.23−2.36 (m, 1H), 2.89−3.00 (m, 2H), 3.03−3.12 (m, 1H), 3.19−3.26 (m, 1H), 3.33−3.41 (m, 1H), 3.56−3.62 (m, 1H), 3.99−4.07 (m, 1H), 7.21−7.38 (m, 5H). Anal. Calcd for $C_{13}H_{17}NO_2 \cdot 0.5(C_2HF_3O_2)$ (276.30): C, 60.86; H, 6.38; N, 5.07. Found: C, 60.86; H, 6.53; N, 4.98.

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