TRIFLUOROACETYLATION OF METHYLPYRIDINES AND OTHER METHYLAZINES: A CONVENIENT ACCESS TO TRIFLUOROACETONYLAZINES

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Abstract ---Treatment of methyl substituted azines, such as pyridine, pyrimidine, quinoline, oxazole, benzoxazole, benzimidazole, and benzothiazole, with trifluoroacetic anhydride in the presence of pyridine at room temperature gave the corresponding trifluoroacetonyl substituted azines in good yields.

For several years, we have been interested in the synthesis and biological activities of heteroaromatic trifluoromethyl ketones.[1] Usually, condensation of α-alkylated heterocycles with some electrophiles has been performed under anhydrous conditions in the presence of a strong base such as BuLi, PhLi, LDA, or $NaNH_2$ in NH_3.[2] The electrophiles reported include anhydrides, esters, aldehydes, ketones, unsaturated ketones, alkyl halides, epoxides and so on. However, the previous methods for trifluoroacetylation of 2-methylpyridine (**1a**) have been reported to furnish 2-trifluoroacetonylpyridine (**2a**) in very poor yields (16-30%).[3] We report here a convenient and alternative method for the synthesis of trifluoroacetonyl substituted azines without using strong bases.

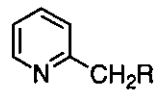
During the course of our studies on the Dakin-West reaction of *N*-acyl-*N*-alkyl-α-amino acids employing trifluoroacetic anhydride (TFAA),[4] we noticed the formation of 2-trifluoroacetonyl-6-methylpyridine (**2c**) from 2,6-dimethylpyridine (**1c**), which was used as a base in the Dakin-West reaction. The compound (**2c**) must be produced by trifluoroacetylation of the methyl group in 2,6-dimethylpyridine. This finding prompted us to investigate the reaction of methyl substituted azines with TFAA more closely and to make it a more efficient method for the synthesis of trifluoroacetonylazines by the trifluoroacetylation of methyl substituted azines.

Thus, treatment of 2-methylpyridine (**1a**) (3 mmol) with TFAA (9 mmol) in benzene in the presence of pyridine (15 mmol) at room temperature resulted in the formation of 2-trifluoroacetonylpyridine (**2a**) in 84% yield (Method A). Reaction variables were examined in the reaction of 2-methylpyridine (**1a**) with TFAA. As shown in Table 1, pyridine promoted the trifluoroacetylation and longer reaction time improved the yield (entry 6). Under these reaction conditions, the trifluoroacetylation of other methyl substituted azines (**1**), such as

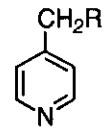
Table 1. Reaction variables of 2-methylpyridine (**1a**) with TFAA in the presence of pyridine.[a]

Entry	TFAA (equiv)[b]	Base (equiv)[b]	Reaction conditions	Yield of **2a** (%)
1	1	none	rt, 2 h; reflux, 6 h	24
2	3	none	rt, 2 h; reflux, 6 h	6
3	0.33	none	rt, 2 h; reflux, 6 h	34[c]
4	3	pyridine (5)	rt, 7 h	59
5	3	K_2CO_3 (3)	rt, 7 h	14
6	3	pyridine (5)	rt, 24 h	84

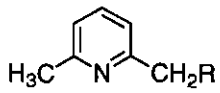
[a] The reactions were carried out on a 3 mmol scale of starting material in benzene.
[b] Equiv. refers to molar equivalents with respect to **1a**. [c] Yield was based on TFAA.



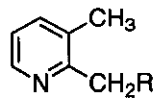
1a: R=H
2a: R=$COCF_3$ (84%)[a]



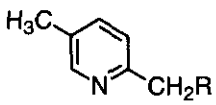
1b: R=H
2b: R=$COCF_3$ (90%)[a]



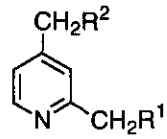
1c: R=H
2c: R=$COCF_3$ (30%)[b]



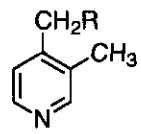
1d: R=H
2d: R=$COCF_3$ (73%)[a]



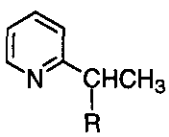
1e: R=H
2e: R=$COCF_3$ (56%)[a]



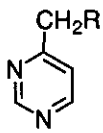
1f: R^1=R^2=H
2f-1: R^1=H, R^2=$COCF_3$ (39)[b]
2f-2: R^1=$COCF_3$, R^2=H (20)[b]



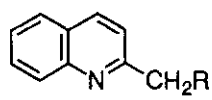
1g: R=H
2g: R=$COCF_3$ (53)[b]



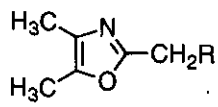
1h: R=H
2h: R=$COCF_3$ (75%)[a]



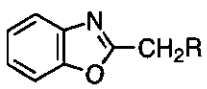
1i: R=H
2i: R=$COCF_3$ (81%)[a]



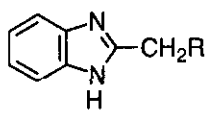
1j: R=H
2j: R=$COCF_3$ (47%)[a]



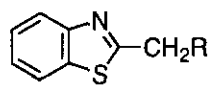
1k: R=H
2k: R=$COCF_3$ (82%)[a]



1l: R=H
2l: R=$COCF_3$ (80%)[a]



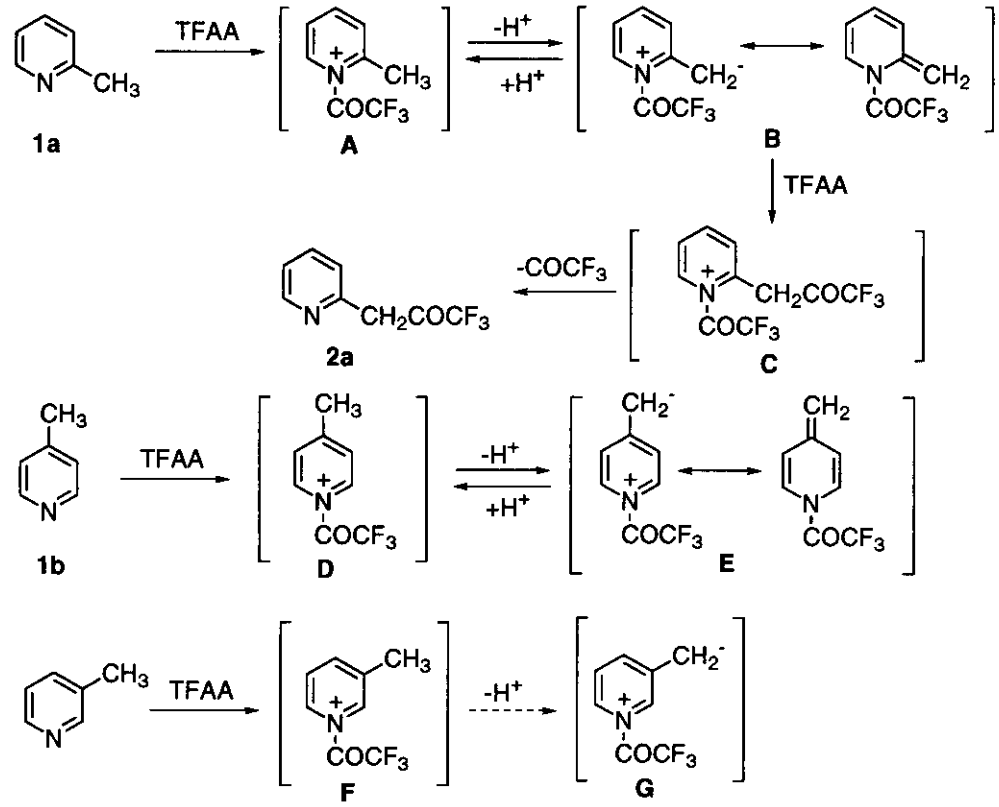
1m: R=H
2m: R=$COCF_3$ (91%)[a]



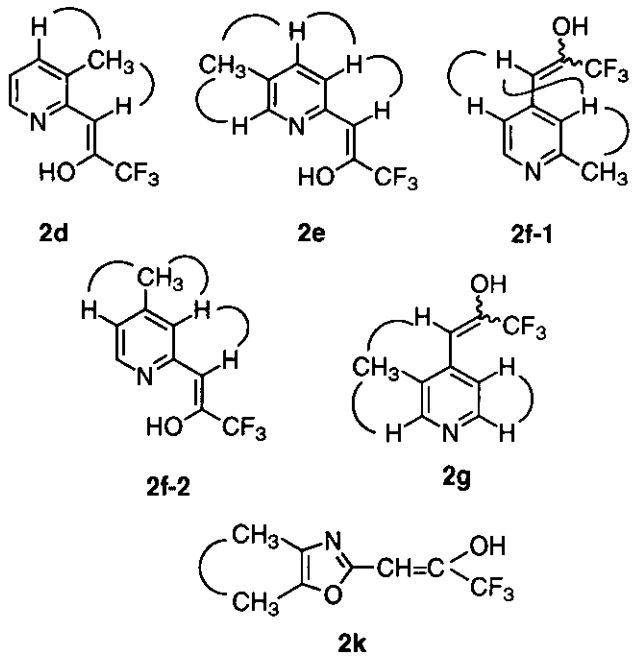
1n: R=H
2n: R=$COCF_3$ (81%)[a]

a: Method A, b: Method B

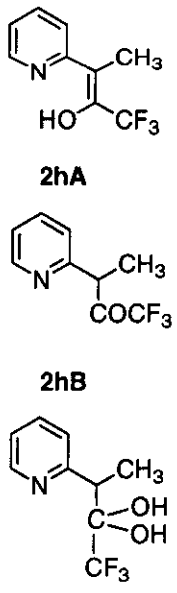
Scheme 1



Scheme 2



Scheme 3. NOE experiments in some trifluoroacetonylazines.



Scheme 4

pyrimidine, quinoline, oxazole, benzoxazole, benzimidazole, and benzothiazole, was exploited and the results are summarized in Scheme 1.

In order to confirm the relative reactivity of the methyl groups, reactions of a series of methyl and dimethyl substituted pyridines (**1a-g**) were examined under the same conditions. The reactivity of methyl substituted pyridine derivatives was at first tested. Among three methylpyridines, 2- (**1a**) and 4-methylpyridine (**1b**) gave the 2- (**2a**) and 4-trifluoroacetonylpyridine (**2b**) in high yields, respectively, whereas 3-methylpyridine failed to react with TFAA under the same conditions. It is known that *N*-quaterization or *N*-oxidation of a pyridine derivative increased to a great extent the acidity of α-hydrogens of the methyl group on 2- and 4-positions of pyridine.[5,6] When the trifluoroacetylation took place at the nitrogen of the methylpyridine, 2- and 4-methyl groups are sufficiently acidic and proton abstraction of the methyl group could be effected by the trifluoroacetate ion (Scheme 2). Therefore, the tautomeric forms **B** and **E** can undergo trifluoroacetylation at the methylene group. On the other hand, the isomerization of *N*-trifluoroacetyl-3-methylpyridinium (**F**) is not possible and the 3-methyl group can not undergo the trifluoroacetylation. Next, the reactivity of five dimethylpyridines was investigated. Both 2,3- (**1d**) and 2,5-dimethylpyridine (**1e**) reacted selectively with TFAA at its 2-methyl group to be converted to 2-trifluoroacetonylpyridine derivatives (**2d** and **2e**). Under similar conditions, trifluoroacetylation of 2,6- (**1c**), 2,4- (**1f**), and 3,4-dimethylpyridine (**1g**) failed and the starting materials were mostly recovered. However, treatment of **1c**, **1f**, and **1g** with 0.5 equiv. of TFAA in benzene under reflux for 6 h afforded the corresponding trifluoroacetonylpyridines in moderate yields (Method B). In these cases, pyridine was not used as the base because addition of pyridine lowered the yields. According to the literature,[2d] 2,4-dimethylpyridine (**1f**) reacts selectively with ethyl benzoate and perfluoroalkyl esters at its 2- or 4- methyl group depending on the condensing agent. It is also reported that 4-methyl hydrogens are more reactive than 2-methyl ones in free bases, whereas the reverse order was demonstrated in the exchange rates of *N*-methiodide and *N*-oxides.[5] In our case, 4-trifluoroacetonyl-2-methylpyridine (**2f-1**) and 2-trifluoroacetonyl-4-methylpyridine (**2f-2**) were obtained in 39 and 20% yields, respectively.

The structure determinations of products (**2**) were performed by spectral data. Each of the ^{1}H NMR spectra of **2**, except for **2h**, shows the presence of a vinylic proton and an enolic proton, thus indicating the presence of a -CH=C(OH)CF_3 functional group. However, the enolic protons were not observed in **2c**, **2f-2**, **2i**, **2j**, and **2m**. The enolic form is stabilized by resonance and by the formation of an intramolecular hydrogen bond. All the products (**2**), except for **2h**, exist in the enol form. The positions of trifluoroacetylation of the methyl group in **1d-g** were determined by the nuclear Overhauser effect (NOE) of the vinyl proton caused by irradiation of this group (Scheme 3). The structure of **2k** was also confirmed by NOEs between the two methyl protons at 2.09 ppm and 2.23 ppm. In the product (**2h**), two tautomeric structures (**2hA** and **2hB**) and one hydrated structure (**2hC**) can be considered : the enol form (**2hA**), the keto form (**2hB**), and the hydrate form (**2hC**) exist in 6 : 3 : 1 ratio (Scheme 4). The ^{1}H-NMR spectrum follows: a quartet (J_{H-F}=1.8) at 2.08 ppm due to the methyl

proton for **2hA**, *two doublets at 1.42 ppm and 1.56 ppm due to the methyl proton for* **2hB** and **2hC**, two quartets at 3.37 ppm and 4.41 ppm due to the methine proton for **2hB** and for **2hC**, respectively.

In conclusion, a simple and general one-pot synthesis of trifluoroacetonyl substituted azines (**2**) from methylazines (**1**) has been devised. The method appears to be useful and convenient in terms of operational simplicity and the mild conditions.

EXPERIMENTAL

M.p.s were determined on a Yanagimoto hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were measured at 500 MHz with tetramethylsilane (Me_4Si) as an internal reference. *J*-Values are given in Hz. IR spectra were recorded on a JASCO IR810 spectrophotometer. Only pertinent IR peaks are given. MS spectra (electron impact: 70 eV) were measured with a JEOL JMS-DS300 spectrometer. For column chromatography, SiO_2 (Merck, Art 9385) was used.

General Procedure for the Reactions of the Azines (1) with TFAA. Method A for 1a, 1b, 1d, 1e, and 1h-n: TFAA (1.3 mL, 9 mmol) was added dropwise to a solution of an azine (3 mmol) and pyridine (1.2 mL, 15 mmol) in anhydrous benzene (8 mL) at 0 °C. The mixture was then stirred at rt for 24 h. The reaction mixture was diluted with 3% Na_2CO_3 (30 mL) and extracted with EtOAc (40 mL x 2). The combined extracts were washed with brine (*30 mL*), *dried over* Na_2SO_4, *filtered, and concentrated under reduced pressure.* Recrystallization or chromatography on silica gel gave the pure product (**2**).

Method B for 1c, 1f, and 1g: TFAA (0.7 mL, 5 mmol) was added dropwise to a solution of an azine (10 mmol) in anhydrous benzene (10 mL) at 0 °C. The mixture was then refluxed for 6 h and cooled in an ice bath. After the same work-up as described above, the pure product was obtained by recrystallization or chromatography on silica gel.

1,1,1-Trifluoro-3-(2-pyridyl)-2-propanone (2a): Yield 84% (after column chromatography)(EtOAc-hexane=1:1): mp 112-113 °C (hexane)(lit.,[3a] mp 116 °C).

1,1,1-Trifluoro-3-(4-pyridyl)-2-propanone (2b): Yield 90% (after column chromatography)(EtOAc-hexane=1:1): mp 168-170 °C (AcOEt), Anal. Calcd for $C_8H_6NOF_3$: C, 50.80; H, 3.20; N, 7.41. Found: C, 50.64; H, 3.34; N, 7.51. MS m/z 189 (M^+, 83), 92 (100); IR υ_{max}/nujol (cm^{-1}) 1650, 2600 (br); ^{1}H NMR (DMSO-d_6) δ 5.43 (s, 1H), 7.93 (d, 4H, *J*=6.7), 12.78 (br s, 1H); ^{13}C NMR (125 MHz) δ 93.49 (CH), 120.51 (C), 123.99 (CF_3, $^1J_{CF}$=293.7), 142.17 (CH), 160.32 (CH), 174.18 (C, $^2J_{CF}$≈27.9).

1,1,1-Trifluoro-3-[2-(6-methylpyridyl)]-2-propanone (2c): Yield 30% (after column chromatography)(EtOAc-hexane=1:1): mp 58-59 °C (hexane), Anal. Calcd for $C_9H_8NOF_3$: C, 53.21; H, 3.97; N, 6.89. Found: C, 52.85; H, 3.97; N, 6.89. MS m/z 203 (M^+, 61), 134 (100); IR υ_{max}/nujol (cm^{-1}) 1680, 3000 (br); ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 5.77 (s, 1H), 6.82 (d, 1H,

J=7.6), 6.90 (d, 1H, *J*=7.6), 7.62 (t, 1H, *J*=7.6).

1,1,1-Trifluoro-3-[2-(3-methylpyridyl)]-2-propanone (2d): Yield 73% (after column chromatography)(EtOAc-hexane=1:1): mp 124-126 °C (AcOEt-hexane), Anal. Calcd for $C_9H_8NOF_3$: C, 53.21; H, 3.97; N, 6.89. Found: C, 53.21; H, 4.23; N, 6.95. MS m/z 203 (M^+, 71), 106 (100); IR υ_{max}/nujol (cm^{-1}) 1670, 3350 (br); ^1H NMR (DMSO-d_6) δ 2.28 (s, 3H), 5.72 (s, 1H), 6.92 (dd, 1H, *J*=6.4, 7.3), 7.56 (d, 1H, *J*=7.3), 7.88 (d, 1H, *J*=6.4), 16.52 (br s, 1H).

1,1,1-Trifluoro-3-[2-(5-methylpyridyl)]-2-propanone (2e): Yield 56% (after column chromatography)(EtOAc-hexane=1:1): mp 120-121 °C (hexane), Anal. Calcd for $C_9H_8NOF_3$: C, 53.21; H, 3.97; N, 6.89. Found: C, 52.98; H, 4.07; N, 6.92. MS m/z 203 (M^+, 74), 134 (100); IR υ_{max}/nujol (cm^{-1}) 1650, 3400 (br); ^1H NMR (DMSO-d_6) δ 2.26 (s, 3H), 5.76 (s, 1H), 7.32 (br s, 1H), 7.79 (dd, 1H, *J*=1.8, 8.8), 8.12 (s, 1H).

1,1,1-Trifluoro-3-[4-(2-methylpyridyl)]-2-propanone (2f-1): Yield 39% (Recrystallized from EtOAc-hexane): mp 173-177 °C, Anal. Calcd for $C_9H_8NOF_3$: C, 53.21; H, 3.97; N, 6.89. Found: C, 52.96; H, 4.10; N, 6.82. MS m/z 203 (M^+, 86), 106 (100); IR υ_{max}/nujol (cm^{-1}) 1630, 1655, 2300-3000 (br); ^1H NMR (DMSO-d_6) δ 2.33 (s, 3H), 5.32 (s, 1H), 6.50-7.25 (br, 1H), 7.81 (d, 1H, *J*=6.7), 8.00-8.60 (br, 1H).

1,1,1-Trifluoro-3-[2-(4-methylpyridyl)]-2-propanone (2f-2): Yield 20% (after column chromatography)(EtOAc-hexane=1:1): mp 128-130 °C (AcOEt-hexane)(lit.,[2d] mp. 130.5-131.2 °C), MS m/z 203 (M^+, 67), 134 (100); IR υ_{max}/nujol (cm^{-1}) 1645, 2500-3100 (br); ^1H NMR (DMSO-d_6) δ 2.38 (s, 3H), 5.72 (s, 1H), 6.83 (d, 1H, *J*=7.6), 6.87 (s, 1H), 7.87 (d, 1H, *J*=7.6).

1,1,1-Trifluoro-3-[4-(3-methylpyridyl)]-2-propanone (2g): Yield 53% (after column chromatography)(EtOAc-hexane=1:1): mp 164-167 °C (AcOEt), Anal. Calcd for $C_9H_8NOF_3$: C, 53.21; H, 3.97; N, 6.89. Found: C, 53.23; H, 4.02; N, 6.95. MS m/z 203 (M^+, 84), 106 (100); IR υ_{max}/nujol (cm^{-1}) 1645, 2300-3000 (br); ^1H NMR (DMSO-d_6) δ 2.05 (s, 3H), 5.21 (s, 1H), 7.88 (s, 1H), 7.89 (d, 1H, *J*=7.0), 8.71 (d, 1H, *J*=7.0), 12.50-12.80 (br, 1H).

1,1,1-Trifluoro-3-(2-pyridyl)-2-butanone (2h): Yield 75% (after column chromatography)(EtOAc-hexane=1:2): mp 60-62 °C (hexane), Anal. Calcd for $C_9H_8NOF_3$: C, 53.21; H, 3.97; N, 6.89. Found: C, 52.92; H, 4.05; N, 6.87. MS m/z 203 (M^+, 63), 106 (100); IR υ_{max}/nujol (cm^{-1}) 1630; ^1H NMR ($CDCl_3$) δ 1.42 and 1.56 (d, 3H, *J*=7.0), 2.08 (q, 3H, $J_{H\text{-}F}$=1.8), 3.37 and 4.41(q, 1H, *J*=7.0), 7.22-7.25 and 7.24-7.28 (m, 2H), 7.37 (d, 1H, *J*=8.5), 7.71 and 7.71 (t, 1H, *J*=7.6), 7.83 (t, 1H, *J*=7.6), 8.27 (d, 1H, *J*=5.2), 8.47 and 8.55 (d, 1H, *J*=5.2).

1,1,1-Trifluoro-3-(4-pyrimidyl)-2-propanone (2i): Yield 81% (Recrystallized from EtOAc-hexane): mp 155-158 °C, Anal. Calcd for $C_7H_5N_2OF_3$: C, 44.22; H, 2.65; N, 14.73. Found: C, 44.31; H, 2.81; N, 14.74. MS m/z 190 (M^+, 54), 121 (100); IR υ_{max}/nujol (cm^{-1}) 1635, 3400 (br); ^1H NMR ($CDCl_3$ + DMSO-d_6, 5:1) δ 5.50 (s, 1H), 6.69 (d, 1H, *J*=5.8), 8.07 (d, 1H, *J*=5.8), 8.46 (s, 1H).

1,1,1-Trifluoro-3-(2-quinolyl)-2-propanone (2j): Yield 47% (after column chromatography)(EtOAc-hexane=1:1): mp 125-126 °C (Et_2O), Anal. Calcd for $C_{12}H_8NOF_3$: C, 60.26; H, 3.37; N, 5.86. Found: C, 60.29; H, 3.63; N, 5.86. MS m/z 239 (M^+, 76), 170 (100); IR υ_{max}/nujol (cm^{-1}) 1640; ^1H NMR ($CDCl_3$) δ 5.77 (s, 1H), 6.94 (d, 1H, *J*=9.2), 7.40 (t, 1H, *J*=7.9),

7.53 (d, 1H, *J*=8.6), 7.64 (t, 1H, *J*=7.9), 7.65 (d, 1H, *J*=8.6), 7.89 (d, 1H, *J*=9.2).

1,1,1-Trifluoro-3-[2-(4,5-dimethyloxazolyl)]-2-propanone (2k): Yield 82% (after column chromatography)(EtOAc-hexane=1:1): mp 105-106 °C (AcOEt-hexane), Anal. Calcd for $C_8H_8NO_2F_3$: C, 46.39; H, 3.89; N, 6.76. Found: C, 46.42; H, 3.99; N, 6.51. MS m/z 207 (M^+, 42), 138 (100); IR υ_{max}/nujol (cm^{-1}) 1610, 1700, 3150 (br); ^1H NMR ($CDCl_3$) δ 2.09 (d, 3H, *J*=0.9), 2.23 (d, 3H, *J*=0.9), 5.40-5.74 (br, 1H), 5.85 (s, 1H).

3-(2-Benzoxazolyl)-1,1,1-trifluoro-2-propanone (2l): Yield 80% (Recrystallized from EtOAc-hexane): mp 165 °C (decomp)(lit.,[7] 165-166 °C).

3-(2-Benzimidazolyl)-1,1,1-trifluoro-2-propanone (2m): Yield 91% (Recrystallized from EtOAc-hexane): mp 279-280 °C (decomp) (lit.,[8] 270 °C).

3-(2-Benzothiazolyl)-1,1,1-trifluoro-2-propanone (2n): Yield 81% (Recrystallized from EtOAc-hexane): mp 225 °C (decomp)(lit.,[9] 229 °C).

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