A New Synthesis of 1-(Trifluoromethyl)enamines and 1-(Trifluoromethyl)alkylamines

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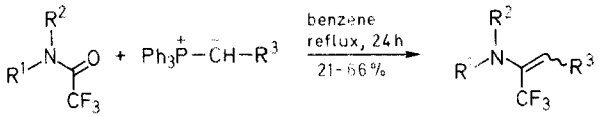
Several 1-(trifluoromethyl)enamines were prepared by heating trifluoroacetamides with alkylidenetriphenylphosphoranes in THF or benzene. The product enamines can be reduced (H_2, Pd/C) to 1-(trifluoromethyl)alkylamines.

The Wittig reaction is a useful approach to aliphatic trifluoromethyl compounds.[1,2,3] Using the same approach as for the synthesis of trifluoromethyl ketones, we now found a versatile and efficient method for the preparation of 1-(trifluoromethyl)-enamines and 1-(trifluoromethyl)alkylamines from various trifluoroacetamides.

N,N-Dialkyltrifluoroacetamides **1** react slowly with alkylidenetriphenylphosphoranes **2** to give 1-(trifluoromethyl)enamines **3** (Table 1) in moderate yield. The configuration (*Z* or *E*) can be assigned on the basis of the differences of the chemical shifts[8]



1 **2** (*Z*)- + (*E*)-**3a-i**

Products	R^1	R^2	R^3
3a, 4a	$(CH_2)_2O(CH_2)_2$		n-C_6H_{13}
3b, 4b	$(CH_2)_2O(CH_2)_2$		Ph
3c, 4c	$(CH_2)_2O(CH_2)_2$		$Ph(CH_2)_2$
3d, 4d	$(CH_2)_5$		c-$C_6H_{11}CH_2$
3e, 4e	$(CH_2)_5$		$Ph(CH_2)_2$
3f	CH_3	$PhCH_2$	n-C_6H_{13}
3g	CH_3	$PhCH_2$	c-$C_6H_{11}CH_2$
3h, 4h	CH_3	$PhCH_2$	$Ph(CH_2)_2$
3i	$PhCH_2$	$PhCH_2$	$Ph(CH_2)_2$
4j	CH_3	H	n-C_6H_{13}
4k	CH_3	H	c-$C_6H_{11}CH_2$
4l	CH_3	H	$Ph(CH_2)_2$
4m	H	H	$Ph(CH_2)_2$

Table 1. Preparation of 1-(Trifluoromethyl)enamines **3**

Product	Yield (%)[a]		Convertion (%)[b]		Ratio (*Z*)-**3** : (*E*)-**3**		bp (°C)/Torr
	Method[c] A	B	Method[c] A	B	Method[c] A	B	
3a	42	76	62	80	43 : 57	46 : 54	132–124/20
3b	62	60	76	76	97 : 3	95 : 05	144/20
3c	66	57	80	77	39 : 61	45 : 55	124/1
3d	21	36	27	55	62 : 38	72 : 28	115/20[d]
3e	46	38	55	42	61 : 39	66 : 34	130/20[d]
3f	53	38	77	57	39 : 61	47 : 53	116/1
3g	55	50	63	65	43 : 57	62 : 38	140/20[d]
3h	37	37	55	53	47 : 53	49 : 51	130/2[d]
3i	23	19	42	42	26 : 74	52 : 48	170/1[d]

[a] Reaction times were usually 24 h except for **3b** (160 h) and **3i** (48 h).
[b] Yield based on starting amide not recovered.
[c] Method of generation of ylide **2** (see Procedures).
[d] Distillation in a bulb-to-bulb short-path apparatus. The temperatures given are oven temperatures, not true boiling points.

and of $^4J_{HF}$ for the *Z*-isomer,[9] detectable at 300 MHz. The *E*-isomer is partially converted into the *Z*-isomer by heating so that the *Z*/*E* ratio does not reflect the stereochemistry of the reaction itself.

This Wittig reaction is less efficient when steric hindrance of the ylid **2** (for example R^3 = cyclohexyl) or the trifluoroacetamide ($R^1 = R^2 = CH_2C_6H_5$) is large.

Catalytic hydrogenation of compounds **3f–i** ($R^2 = CH_2C_6H_5$) under high pressure affords directly the secondary or primary 1-(trifluoromethyl)alkylamines **4j–m**. The tertiary cyclic *N*-[1-(trifluoromethyl)alkyl]amines **4a–e** were obtained in good yield by catalytic hydrogenation of compounds **3a–e** under low pressure. Reduction of the enamine hydrochloride **3** · HCl with $NaBH_3CN$ is also possible but the yields of **4** are lower.

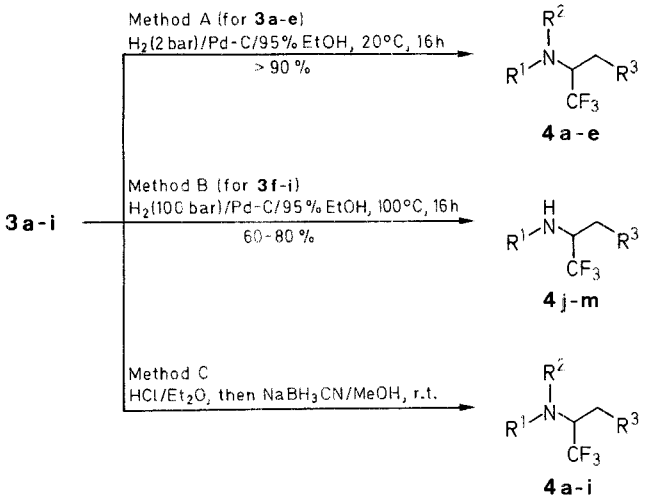


Table 2. Preparation of the 1-(Trifluoromethyl)alkylamine Hydrochlorides **4**·HCl

4 · HCl	Method of Reduction	Yield[a] (a)	Yield[a] (b)	mp (°C)[b]	Molecular Formula[c]
4a	A	71	92	105	$C_{13}H_{25}ClF_3NO$ (303.8)
4b	A	85	93	146	$C_{13}H_{17}ClF_3NO$ (295.7)
4c	A	84	95	143	$C_{15}H_{21}ClF_3NO$
	C	60	72		(323.8)
4d	A	88	90	157–158	$C_{15}H_{27}ClF_3N$ (313.8)
4e	A	87	93	157	$C_{16}H_{23}ClF_3N$ (321.8)
4j	B	74	–	81	$C_{10}H_{21}ClF_3N$ (247.7)
4k	B	67	63	131–132	$C_{11}H_{21}ClF_3N$ (259.7)
4l	B	70	63	115	$Cl_{22}H_{17}ClF_3N$ (267.7)
4m	B	63	48	159–160	$C_{11}H_{15}ClF_3N$ (253.7)

[a] Yield of isolated **4** · HCl after direct work-up (a), or after chromatography of amine **4** (b); yields are calculated on enamines **3**.
[b] Uncorrected, measured with a Mettler FP61 apparatus. The products were recrystallized from MeOH/Et_2O/pentane (2 : 58 : 40).
[c] Satisfactory microanalyses: C ±0.25, H ±0.15, N ±0.10.

In summary, the synthesis reported here represents a useful alternative to the preparation of 1-(trifluoromethyl)alkylamines by known methods[4,5,6,7] via trifluoromethyl ketones.

1-(Trifluoromethyl)enamines 3a–i; General Procedures:

Method A (*Ylide Generation in THF*[10,11]): The phosphonium salt (0.05 mol) and $NaNH_2$ (1.95 g, 0.05 mol) are placed in a flame-dried and argon-flushed three-necked flask and THF (100 mL) is added via syringe through a septum cap. The mixture is vigorously stirred and heated to boiling until no more NH_3 is evolved. The trifluoroacetamide **1** (0.05 mol) is then added to the red ylid solution and heating and stirring are continued until the red color has disappeared (usually 24 h). The mixture is concentrated at reduced pressure and triphenylphosphine oxide is precipitated by the addition of pentane (100 mL). The solution is filtered through a silica gel column (pentane/Et_2O, 97 : 3). Solvents are removed under reduced pressure and the remaining oil is distilled under reduced pressure to give unreacted trifluoroacetamide **1** and then the enamine **3**.

Method B (*Ylide Generation in Benzene*[1]): The phosphonium salt (0.05 mol) and $NaNH_2$ (1.95 g, 0.05 mol) are placed in a flame-dried and argon-flushed three-necked flask. Benzene (20 mL) and hexamethyldisilazan (0.3 mL) are added via syringe through a septum cap. The mixture is vigorously stirred and heated to boiling until no more NH_3 is evolved. Benzene (100 mL) is added, and the red ylid solution is transferred to another flask by syringe; this operation is repeated with benzene (2 × 50 mL). The ylid solution is refluxed (0.5 h), the trifluoroacetamide **1** (0.05 mol) is added, and heating is continued until the red color has disappeared (usually 24 h). The same work-up as in Method A affords unreacted trifluoroacetamide **1** and then the enamine **3**.

1-(Trifluoromethyl)alkylamines 4; General and Typical Procedures:

Method A (*Reduction of Enamines* **3a–e** *to Amines* **4a–e**): A solution of the enamine **3** (4 mmol) in anhydrous EtOH (20 mL) and 5% Pd on coal (1 g, 0.5 mmol) are shaken for 16 h at room temperature in a Parr apparatus under a H_2 pressure of 2.5 bar. The mixture is then taken up in CH_2Cl_2 (60 mL), filtered, and acidified with a 5% solution of HCl in Et_2O (5 mL). This mixture is evaporated under reduced pressure and the remaining crude hydrochloride **4** · HCl is washed with pentane (2 × 30 mL) and recristallized (MeOH/Et_2O/pentane, 2 : 58 : 40). The free amine **4** is obtained from the crude **4** · HCl by stirring with 12 N NaOH (5 mL), followed by extraction with Et_2O (2 × 50 mL); the combined organic extract is washed with brine (10 mL), and dried (Na_2SO_4), and evaporated under reduced pressure. Column chromatography of the residual oil on silica gel (pentane/Et_2O, 98 : 2 as eluent) affords the pure amine **4**.

Method B (*Reduction of Enamines* **3f–k** *to Amines* **4j–m**): A solution of the enamine **3** (4 mmol) in anhydrous EtOH (20 mL) and Pd on activated coal (1 g, 0.5 mmol of Pd) are placed in an autoclave at room temperature, under a H_2 pressure of 140 bar. After 16 h, the mixture is worked up as in Method A.

Method C (*Reduction of Enamine Hydrochlorides* **3** · *HCl with* $NaBH_3CN$:

1,1,1-Trifluoro-2-methylbenzylamino-5-phenylpentane (**4h**); Typical Procedure: A dry 100 mL flask is charged with 1,1,1-trifluoro-2-methylbenzylamino-5-phenyl-2-pentene (**3h**; 1.28 g, 4 mmol) and anhydrous Et_2O (10 mL) and dry HCl is passed through the mixture till complete precipitation of **3h** · HCl. A solution of $NaBH_3CN$ (1.50 g, 24 mmol, 6 equiv) in dry MeOH (5 mL) is quickly added at room temperature. After 30 min, aqueous 1 N NaOH (20 mL) is added and the mixture is extracted with CH_2Cl_2 (3 × 30 mL). The organic extract is washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated. Column chromatography of this crude product on silica gel (pentane/Et_2O, 98 : 2) affords the pure amine **4h**; yield: 920 mg (72%).

The methylbenzylamine **4h** could not be isolated as hydrochloride.

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Table 3. NMR Data of 1-(Trifluoromethyl)enamines **3**

Compound	^{1}H-NMR ($CDCl_3$/TMS)[a] δ or δ_Z/δ_E, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[b] δ or δ_Z/δ_E, J(Hz)	^{19}F-NMR ($CDCl_3/CFCl_3$)[a] δ_Z/δ_E
3a	0.88 (t, 3H, J = 8); 1.3 (m, 8H); 2.2 (m, 2H); 2.78 (m, 4H); 3.7 (m, 4H); 5.85/5.15 (t, 1H, J = 7)	13.7, 22.4, 26.1, 28.6, 29.7/28.8, 31.4, 51.8/51.0, 67.6/67.3, 123.4/122.9 (q, J = 295, CF_3), 131.2/122.0 (q, J = 4.3/2, C̲H−C−CF_3), 138.1/139.6 (q, J = 30, C̲−CF_3)	−64.7/−60.7
3b	2.9 (m, 4H); 3.7 (m, 4H); 6.5/6.2 (s, 1H); 7.25–7.55 (m, 5H)	51.4/50.5, 67.1/66.8, 122.9/119.1 (q, J = 5/2.6, C̲H=C−CF_3), 123.2/122.5 (q, J = 281/275, CF_3), 127.3, 128.4, 128.7, 128.8, 129.8, 133.9, 134.7, 136.1/139.8 (q, J = 30, C̲−CF_3)	−63.5/−59.0
3c	2.6 (m, 8H); 3.65 (m, 4H); 5.9/5.3 (t, 1H, J = 7); 7.3 (m, 5H)	28.7/28.4, 34.4/36.1, 51.8/51.0, 67.5/66.9, 122.7/122.9 (q, J = 274/277, CF_3), 126.1, 128.5, 130.3/120.5 (q, J = 4.5/2, C̲H−C−CF_3), 137.5/140.1 (q, J = 27/30, C̲−CF_3), 141.0	−64.7/−60.7
3d	1.5 (m, 19H); 2.8 (m, 4H); 5.85/5.15 (t, 1H, J = 7)	24.1/23.9, 26.2/26.1, 26.3, 26.4, 26.5, 26.7, 33.2/33.0, 33.9/37.6, 51.9/52.9, 129.1/120.3 (q, J = 4.2/2, C̲H−C−CF_3), 123.4/122.9 (q, J = 281/277.8, CF_3), 138.6/141.6 (q, J = 27/29.3, C̲−CF_3)	−64.5/−60.5
3e	1.7 (m, 6H); 2.5 (m, 8H); 5.8/5.05 (t, 1H, J = 7); 7.1 (m, 5H)	24.2/26.3, 26.9, 28.4, 35.1, 52.1/52.7, 123.5/125.3 (q, J = 281/283, CF_3), 126.1, 128.5, 129.2/119.8 (q, J = 4.5/2, C̲H=C−CF_3), 139.0/141.5 (q, J = 27, C̲−CF_3); 141.4	−64.3/−60.7
3f	0.85 (m, 3H); 1.3 (m, 8H); 2.15 (m, 2H); 2.55/2.4 (s, 3H); 3.95/3.85 (s, 2H); 5.9/5.1 (t, 1H, J = 7); 7.2 (m, 5H)	13.0, 23.6, 27.3, 29.8/29.7, 30.1/31.0, 32.7, 41.0, 61.0/60.5, 124.7/124.3 (q, J = 280/278, CF_3), 128.1, 129.3, 129.4, 129.6, 132.5/124.2 (q, J = 4/1.5, C̲H=C−CF_3), 138.9/140.3 (q, J = 28/29, C̲−CF_3), 140.0/138.6	−63.0/−58.3
3g	1.3 (m, 11H); 2.1 (m, 2H); 2.5 (s, 3H); 3.9 (s, 2H); 5.9/5.1 (t, 1H, J = 7); 7.2 (m, 5H)	26.2/26.3, 26.25/26.4, 32.9, 33.2, 34.2/34.4, 37.5/38.5, 40.3/39.9, 59.4/59.9, 123.6/123.1 (q, J = 280/278, CF_3), 128.15, 128.2, 128.3, 128.5, 130.2/122.2 (q, J = 4/2.4, C̲H−C−CF_3), 137.5, 138.3/139.3 (q, J = 27.6/30, C̲−CF_3)	−62.8/−58.3
3h	2.5 (m, 7H); 3.85 (s, 2H); 5.9/5.1 (t, 1H, J = 7); 7.2 (m, 10H)	28.5, 34.7/36.0, 39.9, 59.6/59.0, 123.4/123.1 (q, J = 276/278, CF_3), 125.9, 127.1, 128.3, 128.5, 130.3/119.5 (q, J = 4/1.5, C̲H=C−CF_3), 137.4, 139.5/142.4 (q, J = 30/25.6, C̲−CF_3), 141.0	−64.3/−60.3
3i	2.35 (m, 4H); 3.9 (s, 4H); 5.9/5.1 (m, 1H); 7.1 (m, 15H)	28.6/28.8, 35.8/34.5, 56.4/55.8, 123.6/123.1 (q, J = 281/278, CF_3), 126.0/125.9, 127.1/127.2, 128.2, 128.25, 128.3, 128.7, 128.9, 132.3/126.2 (q, J = 3.9/1.9, C̲H=C−CF_3), 135.7/136.2 (q, J = 27.8/30, C̲−CF_3), 137.2, 138.4, 141.0	−63.2/−60.7

[a] Recorded on a Varian EM-360A spectrometer.
[b] Recorded on a CFT 20 spectrometer. The signal multiplicities given correlate with C−F coupling.

Table 4. NMR Data of Amines **4**

Compound	^{1}H-NMR ($CDCl_3$/TMS)[a] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[b] δ, J(Hz)	^{19}F-NMR ($CDCl_3/CFCl_3$)[a] δ, J(Hz)
4a	0.9 (m, 3H); 1.35 (m, 12H); 2.75 (m, 5H); 3.6 (t, 4H, J = 5, CH_2O)	14.2, 22.9, 25.5, 26.4, 29.4, 32.1, 50.0, 65.3 (q, J = 25, C̲H−CF_3), 68.0, 127.7 (q, J = 291, CF_3)	−69.5 (d, J = 9)
4b	2.4–3.2 (m, 7H); 3.55 (t, 4H, J = 5, CH_2O); 7.2 (m, $5H_{arom}$)	31.6, 49.6, 67.2 (q, J = 25, C̲H−CF_3), 68.0, 126.4, 126.9 (q, J = 291, CF_3), 128.2, 128.9, 137.9	−69.6 (d, J = 9)
4c	1.7 (m, 4H); 2.7 (m, 7H); 3.6 (t, 4H, J = 5, CH_2O); 7.2 (m, $5H_{arom}$)	24.9, 27.8, 35.5, 49.7, 65.0 (q, J = 25, C̲H−CF_3), 67.8, 126.0, 127.4 (q, J = 291, CF_3), 128.4, 141.9	−69.3 (d, J = 9)
4d	0.9–2.0 (m, 21H); 2.2–3.2 (m, 5H)	23.2, 25.1, 26.6, 26.9, 27.3, 33.3, 33.8, 34.2, 37.7, 50.7, 66.3 (q, J = 24, C̲H−CF_3), 127.9 (q, J = 293, CF_3)	−69.3 (d, J = 9)
4e	1.65 (m, 10H); 2.7 (m, 7H); 7.2 (m, $5H_{arom}$)	24.8, 25.3, 27.1, 27.9, 35.5, 50.4, 65.4 (q, J = 24, C̲H−CF_3), 125.8, 127.7 (q, J = 292, CF_3), 128.3, 142.2	−69.3 (d, J = 9)
4h	1.7 (m, 4H); 2.0–3.3 (m, 6H); 3.75 (m, 2H); 6.9–7.4 (m, $10H_{arom}$)	25.7, 27.7, 35.4, 36.5, 59.2 (s, N−C̲H_2−C_6H_5), 63.3 (q, J = 25, C̲H−CF_3), 127.8 (q, J = 292, CF_3), 125.9, 127.1, 128.4, 128.5, 139.3, 141.9	−67.0 (d, J = 9)
4j	0.8–1.7 (m, 16H); 2.5 (s, 3H, CH_3); 2.8 (m, 1H, CHN)	14.1, 22.9, 25.9, 28.8, 29.4, 29.7, 32.1, 34.9, 61.3 (q, J = 27, C̲H−CF_3), 127.5 (q, J = 284, CF_3)	−75.2 (d, J = 9)
4k	0.8–2.0 (m, 16H); 2.5 (s, 3H, CH_3); 2.9 (m, 1H, CHN)	26.0 (q, J = 1.4, C̲H_2−CH−CF_3), 26.4, 26.8, 33.2, 33.5, 33.6, 34.9, 37.8, 61.5 (q, J = 27, C̲H−CF_3), 127.4 (q, J = 285, CF_3)	−75.2 (d, J = 9)
4l	1.35 (s, 1H, N−H); 1.75 (m, 4H); 2.1–3.3 (m, 6H); 7.2 (m, $5H_{arom}$)	27.4, 29.0, 34.7, 35.6, 60.8 (q, J = 27, C̲H−CF_3), 125.9, 127.1 (q, J = 285, CF_3), 128.4, 141.7	−75.3 (d, J = 9)
4m	1.3 (m, 2H); 1.4–2.0 (m, 4H, CH_2 + NH_2); 2.65 (m, 2H); 3.0 (m, 1H); 7.2 (m, $5H_{arom}$)	27.5, 29.4, 35.6, 53.8 (q, J = 18, C̲H−CF_3), 126.0, 126.8 (q, J = 281, CF_3), 128.5, 141.8	−79.7 (d, J = 9)

[a,b] See Table 3.

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