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Aza-Henry reaction with trifluoropiruvate ketimines

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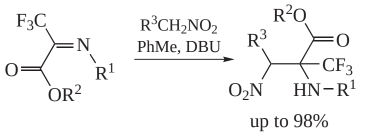
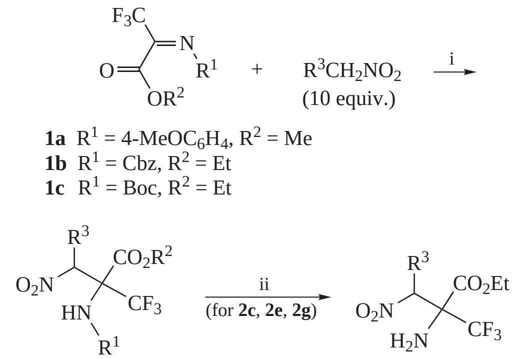
The aza-Henry addition of nitroalkanes at ketimines derived from trifluoropiruvate affords the corresponding α-nitro amines in up to 98% yields.



R^1 = 4-MeOC$_6$H$_4$, Boc, Cbz
R^2 = Me, Et
R^3 = H, Me, Et

Fluorine and perfluoroalkyl groups (especially CF_3) are recognized as important moieties in drugs and drug candidates due to their lipophilicity, high electronegativity and low reactivity.[1] Fluorinated amino acids are in demand as building blocks for drug design because they are a part of many biologically active peptides.[2,3] Selective incorporation of fluorine into peptides results in increased chemical and methabolic stability with simultaneously enhanced hydrophobicity.[4] However, the range of available fluorinated amino acids is limited, therefore, convenient synthetic methods for their preparation are required. This work is an extension of our investigation of the aza-Henry reaction with trifluoromethylated ketimines[5] and is devoted to the aza-Henry reaction of ketimines derived from trifluoropyruvate.

Trifluoropyruvate imines **1a**–**c** are highly electrophilic substrates because of two acceptors (trifluoromethyl and carboxylic groups) in their structure. Considering this feature, we developed a synthesis of the corresponding α-nitro amines **2** (Scheme 1). Addition of methyl 3,3,3-trifluoro-2-(4-methoxyphenylimino)-propanoate **1a** onto nitromethane was investigated as a model reaction (Table 1, entry 1). To find optimal conditions for the reaction, catalytic systems ($ZnCl_2$ + Pr^i_2NEt, $BF_3{\cdot}Et_2O$ + K_2CO_3, DBU, DBN, DABCO, K_2CO_3, KOH, CsF, Pr^i_2NEt, DBU + $ZnCl_2$), solvents (toluene, acetonitrile, DMF, THF, methanol, nitromethane) and the reagent ratio were varied. Only strong organic bases such as DBU and DBN allowed us to obtain the target product **2a**. In polar solvents and large excess of nitromethane, plenty of by-products were formed and the yields of **2a** did not exceed 15%. In case of catalytic amounts of DBU, the reaction was slow and did not reach completion while degradation of formed nitroamine **2a** took place. To accelerate the reaction, we used 1 equiv. of DBU. The optimal conditions comprise the application of 10 equiv. of nitromethane, 1 equiv. of DBU, and toluene as a solvent thus providing the 98% yield of **2a**. In the presence of DBN, the yield was lower (65%).



1a R^1 = 4-MeOC$_6$H$_4$, R^2 = Me
1b R^1 = Cbz, R^2 = Et
1c R^1 = Boc, R^2 = Et

2a R^1 = 4-MeOC$_6$H$_4$, R^2 = Me, R^3 = H
2b R^1 = Cbz, R^2 = Et, R^3 = H
2c R^1 = Boc, R^2 = Et, R^3 = H
2d R^1 = Cbz, R^2 = Et, R^3 = Me
2e R^1 = Boc, R^2 = Et, R^3 = Me
2f R^1 = Cbz, R^2 = R^3 = Et
2g R^1 = Boc, R^2 = R^3 = Et

3a R^3 = H
3b R^3 = Me
3c R^3 = Et

Scheme 1 *Reagents and conditions*: i, DBU (1 equiv.), PhMe, ~20 °C, 1 h; ii, HCl, MeOH.

The target nitroamines **2a**–**c** are formed within an hour,[†] the further prolongation causes rapid destruction of the product: after 3 h nothing of compounds **2a**–**c** is observed. It is important to note that imines **1b** and **1c** containing the acceptor group

Table 1 Aza-Henry reaction of trifluoropyruvate imines with nitroalkanes.

Entry	Imine	Nitroalkane	Product	Yield (%)
1	**1a**	$MeNO_2$	**2a**	98
2	**1b**	$MeNO_2$	**2b**	85
3	**1c**	$MeNO_2$	**2c**	91
4	**1b**	$EtNO_2$	**2d**[a]	55
5	**1c**	$EtNO_2$	**2e**[b]	65
6	**1b**	$PrNO_2$	**2f**[b]	40
7	**1c**	$PrNO_2$	**2g**[b]	44

[a] Two diastereomers (10 : 1). [b] Two diastereomers (1 : 1).

[†] *General procedure for aza-Henry reaction*. Nitroalkane [10 mmol, nitromethane (0.535 ml), nitroethane (0.500 ml) or nitropropane (0.890 ml)] and DBU (1 mmol, 152 μl) were added to a solution of ketimine **1a**–**c** (1 mmol) in toluene (4 ml). The mixture was kept at room temperature for 1 h (TLC control, eluent hexane–dichloromethane, 3 : 1). The mixture was concentrated under reduced pressure, and products **2a**–**g** were isolated by column chromatography using hexane–dichloromethane (1 : 1).

Methyl 3,3,3-trifluoro-2-(4-methoxyphenylamino)-2-(nitromethyl)-propanoate **2a**, yield 98%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78 (s, 3H, MeO), 3.99 (s, 3H, MeO), 4.83 (br. s, 1H, NH), 5.01 (d, 1H, CH_2, $^2J_{HH}$ 15.9 Hz), 5.14 (d, 1H, CH_2, $^2J_{HH}$ 15.9 Hz), 6.80–6.81 (m, 2H, Ar), 6.92–6.94 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.0 (MeO), 66.4 (q, CCF_3, $^2J_{CF}$ 27.1 Hz), 70.8 (CH_2NO_2), 114.1 (Ar), 122.2 (q, CF_3, $^1J_{CF}$ 289.0 Hz), 125.3 (Ar), 133.0 (C_q, Ar), 114.1 (C_q, Ar), 156.3 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$) δ: –73.87 (CF_3). IR (neat, ν/cm^{-1}): 3000 (br. s, NH), 1750 (CO). MS (ESI), m/z: 345.0666 (calc. for $C_{12}H_{13}F_3N_2NaO_5$, m/z: 345.0669 [M + Na]$^+$).

on the nitrogen atom are more reactive than imine **1a** and side reactions proceed more actively in the former case. Nevertheless, compounds **2b** and **2c** were prepared in 85–91% yields (Table 1, entries 2, 3).

To evaluate scope and limitations, we tested other nitroalkanes (see Scheme 1). Imines **1b** and **1c** easily reacted with nitroethane and nitropropane to give nitroamines **2d–g** in good yields as mixtures of diastereomers (see Table 1, entries 4–7). In the case of nitroamine **2e**, diastereomers can be separated. Meanwhile, reaction of imine **1a** with $EtNO_2$ and $PrNO_2$ was unsuccessful despite our efforts to find the conditions.

We also demonstrated possibility of Boc-deprotection at amino group in adducts **2c**,**e**,**g**. For this purpose, the latter were treated with methanolic hydrogen chloride (see Scheme 1) to afford the desired α-nitro amines **3a–c** in quantitative yields after simple evaporation of methanol.

In conclusion, aza-Henry reaction between trifluoropyruvate ketimines and nitroalkanes was investigated. The target α-nitro amines were prepared in good (for nitroethane and nitropropane) and high (for nitromethane) yields. Subsequent deprotection of amino group makes possible its further functionalization.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.03.006.

Ethyl 2-benzyloxycarbonylamino-3,3,3-trifluoro-2-(nitromethyl)-propanoate **2b**, yield 85%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *Me*CH_2, $^3J_{HH}$ 7.3 Hz), 4.43 (q, 2H, MeCH_2, $^3J_{HH}$ 7.3 Hz), 5.12 (s, 2H, CH_2), 6.23 (s, 2H, CH_2), 7.35–7.39 (m, 5H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.2 (*Me*CH_2), 27.8 (MeCH_2), 63.1 (q, *C*CF_3 $^2J_{CF}$ 30.2 Hz), 64.4 (CH_2), 67.3 (CH_2NO_2), 117.9 (q, CF_3, $^1J_{CF}$ 283.5 Hz), 127.8 (Ar), 128.2 (Ar), 132.2 (Ar), 134.8 (C_q, Ar), 153.5 (C=O), 163.1 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$) δ: –74.69 (CF_3). IR (neat, ν/cm^{-1}): 3225 (br.s, NH), 1680 (CO), 1720 (CO). Found (%): C, 46.36; H, 4.34; N, 7.88. Calc. for $C_{14}H_{15}F_3N_2O_6$ (%): C, 46.16; H, 4.15; N, 7.69.

*Ethyl 2-*tert*-butoxycarbonylamino-3,3,3-trifluoro-2-(nitromethyl)-propanoate* **2c**, yield 91%, yellowish-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (t, 3H, *Me*CH_2, $^3J_{HH}$ 7.3 Hz), 1.43 (s, 9H, 3Me), 4.41 (q, 2H, MeCH_2, $^3J_{HH}$ 7.3 Hz), 5.15–5.19 (m, 2H, CH_2), 5.93 (br.s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.2 (Me), 27.6 (Me), 61.0 (q, *C*CF_3, $^2J_{CF}$ 28.2 Hz), 64.4 (CH_2–O), 70.0 (*C*Me), 81.4 (CH_2NO_2), 124.8 (q, CF_3, $^1J_{CF}$ 293.7 Hz), 152.8 (C=O), 163.4 (C=O). ^{19}F NMR (375 MHz, $CDCl_3$) δ: –74.71 (CF_3). IR (neat, ν/cm^{-1}): 3345 (br.s, NH), 1780 (CO), 1670 (CO). Found (%): C, 40.18; H, 5.23; N, 8.52. Calc. for $C_{11}H_{17}F_3N_2O_6$ (%): C, 40.00; H, 5.19; N, 8.48.

For characteristics of compounds **2d**–**g**, see Online Supplementary Materials.

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