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Unusual condensation of 1,1,1,5,5,5-hexafluoropentane-2,4-dione with (*R*)-phenylglycinol

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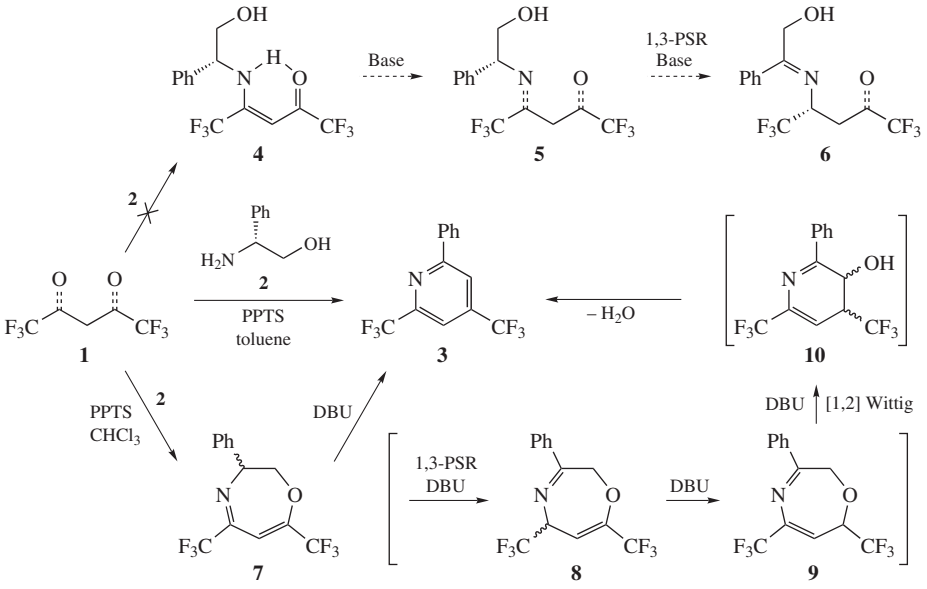
The reaction of 1,1,1,5,5,5-hexafluoropentane-2,4-dione with (*R*)-phenylglycinol proceeds *via* the intermediate formation of (*R*,4*E*,6*Z*)-5,7-bis(trifluoromethyl)-2,3-dihydro-3-phenyl-1,4-oxazepine, which further undergoes a base-catalysed 1,3-proton shift followed by [1,2] Wittig rearrangement giving rise to 2,4-bis(trifluoromethyl)-6-phenylpyridine.

Recently, the synthesis of fluorine-containing heterocyclic compounds has received a great deal of attention due to their increasing applications in medicine and agrochemistry.[1,2] A general and well-developed method for the preparation of fluorine-containing heterocycles is the condensation of fluorinated 1,3-diketones with hydrazines, hydroxylamine, urea, thiourea, guanidine, and substituted anilines furnishing corresponding pyrazoles, isoxazoles, pyrimidines and quinolines.[1–3] In particular, the reactions of 1,1,1,5,5,5-hexafluoropentane-2,4-dione **1** with amino compounds are used for the preparation of nitrogen heterocycles



Scheme 1

containing two trifluoromethyl groups.[1,2,4–12] For instance, we described a convenient method for the preparations of diastereomerically pure trifluoromethyl-containing myosmines [3,5-bis(trifluoromethyl)-4,5-dihydro-2-(pyridin-2-yl)-3*H*-pyrrol-3-ols] *via* a reaction between 2-(aminomethyl)pyridine and pentane-2,4-dione **1**.[13] Here, we describe a condensation reaction between (*R*)-phenylglycinol **2** and pentanedione **1** which unexpectedly produced 2,4-bis(trifluoromethyl)-6-phenylpyridine **3** (Scheme 1) as a sole reaction product.

In our studies on the 1,3-proton shift reaction (1,3-PSR),† we systematically investigated condensation reactions of pentanedione **1** with achiral and chiral benzylamine derivatives.[20] In particular, for asymmetric biomimetic transamination of a carbonyl group in pentanedione **1**, we reacted compound **1** with amino alcohol **2** to prepare enamine **4**, which was expected to undergo base-catalysed 1,3-PSR through intermediate Schiff base **5** giving rise to target imine **6** (Scheme 1). Unexpectedly, the reaction of pentanedione **1** with amino alcohol **2** under standard Dean–Stark conditions with pyridinium *p*-toluenesulfonate as a catalyst gave rise to bis(trifluoromethyl)pyridine **3** in 54% isolated yield.

Pyridine **3** was fully characterised by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy.‡ Puzzling over a plausible mechanism for the formation of pyridine **3**, we focused affords on isolation of any possible intermediates which would give us a valuable clue to a possible sequence of transformations leading to compound **3**. To this end, we conducted a series of reactions between pentanedione **1** and amino alcohol **2** under various conditions carefully controlling the composition of reaction mixtures by TLC and ^{19}F NMR spectroscopy. Fortunately, conducting the reaction under mild conditions (chloroform instead of toluene as a solvent), we detected and isolated (37.8% yield) (*R*,4*E*,6*Z*)-5,7-bis(trifluoromethyl)-2,3-dihydro-3-phenyl-1,4-oxazepine **7**, which is apparently a product of direct condensation between **1** and **2** and the precursor of pyridine **3**. Thus, isolated and chemically pure oxazepine **7** was submitted to the original reaction conditions (toluene as a solvent and pyridinium *p*-toluenesulfonate as a catalyst under reflux). Within 3 h of the reaction, compound **7** was completely consumed giving rise to pyridine **3** and some decomposition products. With oxazepine **7** in hand as an intermediate, we can suggest the following sequence of transformations leading to the formation of pyridine **3**. First, oxazepine **7** undergoes base-catalysed 1,3-PSR giving rise to imine **8**. The latter undergoes a second base-catalysed 1,3-proton transfer leading to conjugated 2-azadiene **9**. The transformation of azadiene **9** to compound **10** can be described as [1,2] base-catalysed Wittig rearrangement,[21] followed by dehydration and aromatization of intermediate **10** to final product **3**. Since all of the three reactions are base-catalysed, we anticipated that this sequence of transformations could be conducted under milder conditions in the presence of a relatively strong base, as compared with the original reaction conditions (refluxing in toluene). Indeed, the treatment of oxazepine **7** with DBU at ambient temperature resulted in its clean and relatively fast (2 h) transformation to pyridine **3**, which was isolated in 73.7% yield.

In summary, we found that the condensation of pentanedione **1** with amino alcohol **2** proceeds through the formation of intermediate oxazepine **7**, which easily undergoes two base-catalysed 1,3-proton shifts followed by [1,2] Wittig rearrangement giving rise to bis(trifluoromethyl)pyridine **3**.

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† For key references on 1,3-proton shift reaction, see refs. 14–19.

‡ *Procedure for preparation of 2,4-bis(trifluoromethyl)-6-phenylpyridine* **3**. To the solution of (*R*)-phenylglycinol (0.362 g, 2.6432 mmol) and PPTS (pyridinium *p*-toluenesulfonate) (0.0664 g, 0.2643 mmol) in toluene (4 ml), the toluene (4 ml) solution of 1,1,1,5,5,5-hexafluoropentane-2,4-dione **1** (1.0003 g, 4.8077 mmol) was added at room temperature. The condenser was attached to the reactor and the reaction mixture was refluxed at 150 °C for 3 h. Solvent was removed under reduced pressure and the resultant product was purified by silica gel chromatography (hexane) furnishing compound **3** (0.4155 g, 54.0%). ^{1}H NMR, δ: 8.15–8.00 (m, 3H), 7.8 (s, 1H), 7.58–7.50 (m, 3H). ^{19}F NMR, δ: –64.6 (s, CF_3), –68.1 (s, CF_3). ^{13}C NMR, δ: 159.2, 149.3 (q, *J* 35.3 Hz), 140.6 (q, *J* 34.1 Hz), 136.1, 130.6, 129.0, 127.1, 122.3 (q, *J* 271.5 Hz), 120.9 (q, *J* 272.3 Hz), 118.4 (qm, *J* 3.6 Hz), 114.3 (m).

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