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Rearrangement of 3,5-dicyano-1,4-dihydropyridines to densely functionalized cyclopentadienes

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ABSTRACT

3,5-Dicyano-1,4-dihydropyridines underwent ring contraction to give functionalized cyclopentadienes upon treatment with trifluoroacetic anhydride.

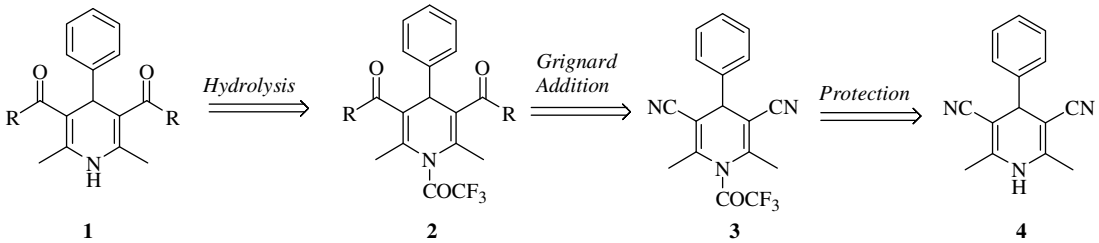
Dihydropyridines (DHPs) have a rich medicinal chemistry.[1] In particular, 4-aryl-substituted 1,4-dihydropyridines are an important class of organic calcium-channel modulators used for the treatment of cardiovascular diseases.[2]

More recently, DHPs were recognized as inhibitors of the permeability-glycoprotein (P-gp).[3] This finding revitalized the interest of the synthetic community in the 1,4-dihydropyridine core.[4]

As a part of our ongoing studies on the synthesis of bioactive compounds,[5] we became interested in preparing 1,4-dihydropyridines **1** bearing two symmetrical ketone functionalities at C-3 and C-5 (Scheme 1). A retrosynthetic analysis of target **1** identified 3,5-dicyanodihydropyridine **4** as a suitable starting material. In our plan, protection of **4** as its *N*-trifluoroacetate **3** and subsequent treatment with a Grignard reagent would furnish the protected target **2**. Then hydrolysis of the trifluoroacetamide in **2** would give the desired compound **1**. Reaction of **3** with various Grignard reagents was identified as a simple and effective means to expand the diversity of scaffold **4**, while the trifluoroacetate group in **3** would activate the two nitrile groups towards nucleophiles.

Compound **4** was prepared using a literature procedure,[6] and then was treated with trifluoroacetic anhydride (TFA) and triethylamine (TEA). Surprisingly, this reaction furnished compound **5** in 43% isolated yield as the exclusive product (Scheme 2). The structure of **5** was determined by X-ray analysis (Fig. 1).[7]

Intrigued by this result, we have studied the reaction of compound **4** with TFA and TEA by ^{1}H NMR. This study revealed that reaction of **4** with TFA generated the desired target **3** in quantitative amounts and in a very short reaction time (Table 1). Typically



1 **2** **3** **4**

Scheme 1.

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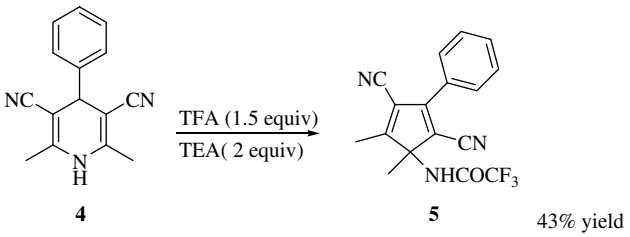


Scheme 2.

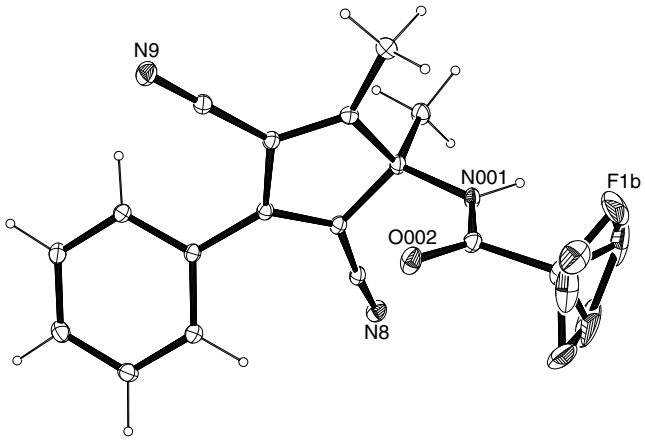
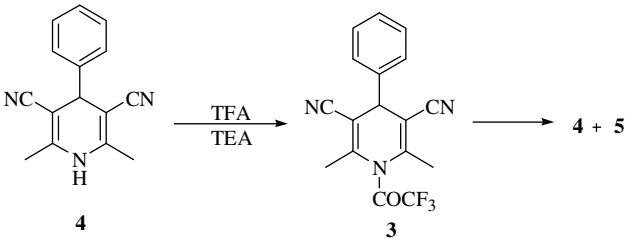


Figure 1. ORTEP drawing of compound **5** with 20% probability thermal ellipsoids.

5–10 min was required to observe full conversion of **4** to **3**. The formation of **3** was also confirmed by GC–MS analysis, which revealed the presence of a molecular ion of mass *m/z* 331 as the main component of the reaction mixture. Compound **3**, however, proved to be unstable and with time underwent ring rearrangement to give cyclopentadiene **5**.

Typically, compound **5** was formed in 40% yield after 5.5 h (Table 1). The yields of **5** were never greater than 40–45%: the remaining **3** underwent hydrolysis to give starting material **4**. Hence, treatment of compound **4** with 1.5 equiv of TFA and 2 equiv of TEA gave initially a quantitative yield of **3** that with time became a 40:60 mixture of compounds **5** and **4** (Table 1, Scheme 3).



Scheme 3.

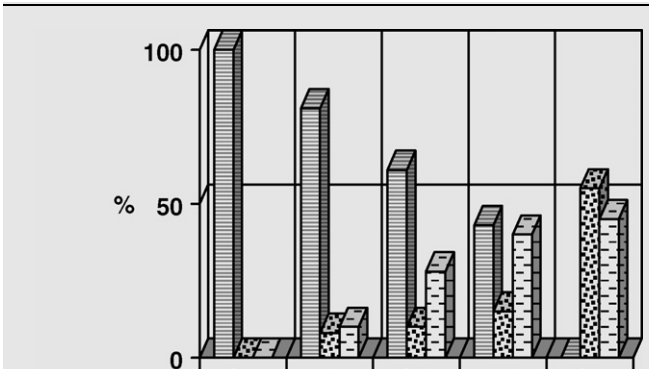
Reaction of **4** with smaller amounts of TFA (1.1 equiv) or larger amounts of TEA gave similar results. The rearrangement of **3** to **5** was operative only when the trifluoroacetamide and the nitrile functionalities were present. Reaction of **4** with acetic anhydride or *p*-toluenesulfonyl chloride did not furnish the rearranged product; similarly, 3,5-dibenzoyl-1,4-dihydropyridine reacted with TFA to give the expected *N*-trifluoroacetamide. A proposed mechanism for the formation of **5** is outlined below (Scheme 4).

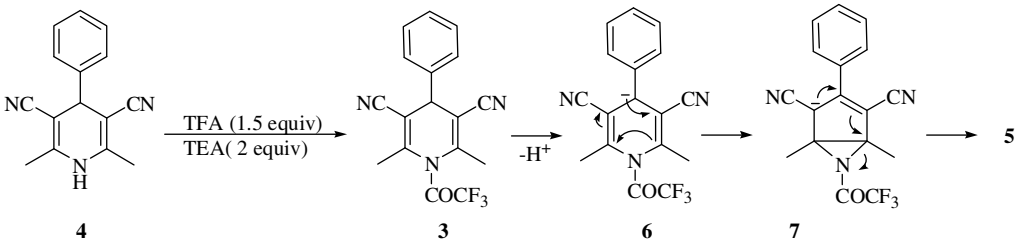
Initial reaction of **4** with TFA furnished **3**. Deprotonation of the benzylic proton in **3** then resulted in the rearrangement. This proposal is supported by the following observations: (a) rearrangement of **3** to **5** was faster when 3 equiv or more of base were used; (b) rearrangement of **3** to **5** did not occur when only one equivalent of base was used; (c) the rearrangement was more efficient with compounds **9**–**10** (Table 2) bearing electron-withdrawing groups on the phenyl ring. We prepared compounds **8**–**11** and submitted them to reaction with TFA and TEA. The yields of **12**–**15** were calculated relative to starting materials **8**–**11** in the crude ^{1}H NMR (Table 2).

As expected based on the proposed mechanism (Scheme 4), conversion of **4** to **5** correlated with the acidity of the benzylic proton. The structure of compound **15** was confirmed by X-ray analysis (Fig. 2).[8]

In conclusion, we have reported a rearrangement of 3,5-dicyano-1,3-dihydropyridines, which furnished highly functionalized cyclopentadienes. The reaction was fast and made use of cheap and commercially available reagents. Considering the versatility of cyclic dienes it is easy to envisage several applications of

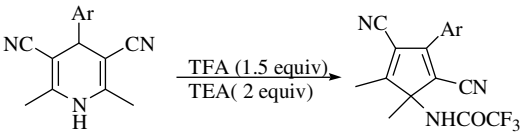
Table 1
^{1}H NMR study of the reaction between **4** and TFA in the presence of TEA





Scheme 4.

Table 2
Preparation of compounds **5** and **12–15**



8-11 **12-15**

Entry	Substrate	Product	Ar	Yield[a] (%)
1	**4**	**5**	C_6H_5	45
2	**8**	**12**	4-CH_3O–C_6H_4	26
3	**9**	**13**	4-NO_2–C_6H_4	63
4	**10**	**14**	2,4-NO_2–C_6H_3	75
5	**11**	**15**	2-Thienyl	23

[a] Calculated by relative integration of the methyl groups in the ^{1}H NMR spectra (400 MHz, $CDCl_3$).

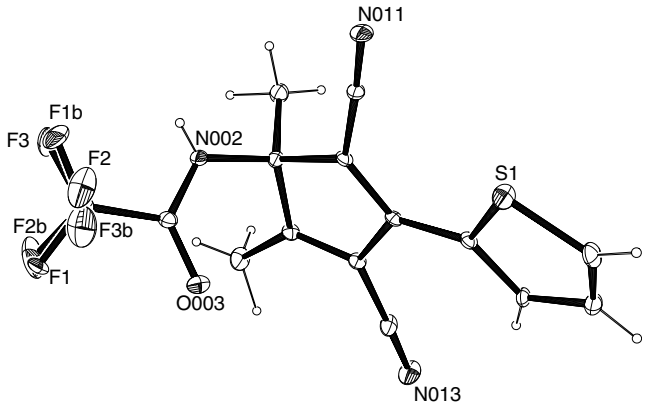


Figure 2. ORTEP drawing of compound **15** with 20% probability thermal ellipsoids.

compounds **5** and **12–15** in synthesis. Studies aimed at obtaining enantiopure samples of **5** by reacting **4** in the presence of chiral amines are in progress.

Preparation of compound **3**: To a solution of 1,4-dihydropyridine **4** (1 mmol) in anhydrous CH_2Cl_2 (10 mL) kept at 0 °C by means of an ice bath were sequentially added anhydrous TEA (2 equiv) and TFA (1.5 equiv). The reaction mixture was then allowed to reach room temperature, and was stirred for 5 min. After this time, the solvent was evaporated, and the oil so obtained was purified by flash chromatography (petroleum ether–ethyl acetate 3:1) to give compound **3** as a colourless solid, 305 mg (92% yield), mp 55–57 °C; δ_H (400 MHz, $CDCl_3$) 2.41 (6H, s, CH_3), 4.34 (1H, s, H-4), 7.18–7.40 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 20.2, 43.5, 102.2, 113.3, 115.8, 126.8, 128.9, 129.6, 136.4, 148.3, 161.8; *m/z* (EI) 331 (M^+, 100%); Anal. Calcd for $C_{17}H_{12}F_3N_3O$: C, 61.63; H, 3.65; N, 12.68. Found: C, 61.55; H, 3.85; N, 12.65.

General procedure for the preparation of compounds **5** *and* **12–15**: To a solution of 1,4-dihydropyridine, **4** or **8–11** (1 mmol) in anhydrous CH_2Cl_2 (10 mL) kept at 0 °C by means of an ice bath, were sequentially added anhydrous TEA (2 equiv) and TFA (1.5 equiv). The reaction mixture was then allowed to reach room temperature, and was stirred for a further 5 h. After this time, the solvent was evaporated, and the oil obtained was purified by column chromatography (petroleum ether–ethyl acetate 4:1) to give compounds **5** or **12–15** as solids.

N-(2,4-Dicyano-1,5-dimethyl-3-phenylcyclopenta-2,4-dienyl)-2′,2′,2′-trifluoroacetamide (**5**): yellow solid, 149 mg (45% yield), mp 205–207 °C; δ_H (400 MHz, $CDCl_3$) 1.62 (3H, s, CH_3), 2.19 (3H, s, CH_3), 6.92 (1H, br s, NH), 7.49–7.79 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 12.9, 21.8, 68.6, 113.2, 113.6, 114.0, 117.5, 127.9, 129.2, 129.3, 131.4, 152.5, 153.9, 170.4; *m/z* (EI) 331 (M^+, 100%); Anal. Calcd for $C_{17}H_{12}F_3N_3O$: C, 61.63; H, 3.65; N, 12.68. Found: C, 61.51; H, 3.91; N, 12.71.

N-(2,4-Dicyano-1,5-dimethyl-3-(4′-methoxyphenyl)cyclopenta-2,4-dienyl)-2′,2′,2′-trifluoroacetamide (**12**): yellow solid, 72 mg (26% yield), mp 185–187 °C; δ_H (400 MHz, $CDCl_3$) 1.60 (3H, s, CH_3), 2.15 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.90 (1H, br s, NH), 7.00 (2H, d, J = 7, Ar), 7.75 (2H, d, J = 7, Ar); δ_C (100 MHz, $CDCl_3$) 12.9, 21.9, 55.5, 68.5, 111.0, 112.8, 113.5, 114.7, 117.8, 121.8, 129.8, 152.7, 155.2, 162.2, 170.5; *m/z* (ESI) 360 ($M-H^+$ 100%); Anal. Calcd for $C_{18}H_{14}F_3N_3O_2$: C, 59.83; H, 3.91; N, 11.63. Found: C, 59.81; H, 3.92; N, 11.66.

N-(2,4-Dicyano-1,5-dimethyl-3-(4′-nitrophenyl)cyclopenta-2,4-dienyl)-2′,2′,2′-trifluoroacetamide (**13**): 218 mg, yellow solid (63% yield), mp 199–200 °C; δ_H (400 MHz, $CDCl_3$) 1.65 (3H, s, CH_3), 2.19 (3H, s, CH_3), 6.91 (1H, br s, NH), 7.89 (2H, d, J = 7, Ar), 8.37 (2H, d, J = 7, Ar); δ_C (100 MHz, $CDCl_3$) 13.1, 21.6, 68.9, 112.0, 112.7, 113.1, 116.53, 124.4, 129.1, 130.0, 135.0, 149.8, 150.9, 171.7; *m/z* (ESI) 375 ($M-H^+$, 100%); Anal. Calcd for $C_{17}H_{11}F_3N_4O_3$: C, 54.26; H, 2.95; N, 14.89. Found: C, 54.32; H, 2.94; N, 14.93.

N-(2,4-Dicyano-1,5-dimethyl-3-(2′,4′-dinitrophenyl)cyclopenta-2,4-dienyl)-2′,2′,2′-trifluoroacetamide (**14**): 286 mg, pale yellow solid (75% yield), mp 190–192 °C; δ_H (400 MHz, $CDCl_3$) 1.63 (3H, s, CH_3), 2.15 (3H, s, CH_3), 7.49 (1H, br s, NH), 7.82 (1H, d, J = 7, Ar), 8.63 (1H, d, J = 7, Ar), 9.13 (1H, s, Ar); δ_C (100 MHz, $CDCl_3$) 14.1, 20.3, 69.2, 111.7, 112.3, 113.4, 116.2, 117.8, 121.2, 129.1, 131.2, 133.5, 146.7, 149.4, 150.2, 168.9; *m/z* (ESI) 420 ($M-H^+$, 100%); Anal. Calcd for $C_{17}H_{10}F_3N_5O_5$: C, 48.47; H, 2.39; N, 16.62. Found: C, 48.56; H, 2.38; N, 16.68.

N-(2,4-Dicyano-1,5-dimethyl-3-(thiophen-2′-yl)cyclopenta-2,4-dienyl)-2′,2′,2′-trifluoroacetamide (**15**): yellow solid, 67 mg (23% yield), mp 250 °C dec.; δ_H (400 MHz, $CDCl_3$) 1.54 (3H, s, CH_3), 2.13 (3H, s, CH_3), 6.64 (1H, br s, NH), 7.18 (1H, app t, J = 6, $H4_{(thiophene)}$), 7.61 (1H, d, J = 6, $H3_{(thiophene)}$), 8.06 (1H, d, J = 6, $H5_{(thiophene)}$); δ_C (100 MHz, $CDCl_3$) 12.9, 21.6, 68.8, 109.8, 111.1, 112.0, 114.6, 128.3, 130.7, 130.9, 132.0, 144.3, 171.8; *m/z* (ESI) 336 ($M-H^+$, 100%); Anal. Calcd for $C_{15}H_{10}F_3N_3OS$: C, 53.41; H, 2.99; N, 12.46. Found: C, 53.23; H, 3.05; N, 12.43.

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8. Data deposited at the Cambridge Crystallographic Data Centre, CCDC 689301.