Pergamon

Tetrahedron Letters 40 (1999) 2541–2544

TETRAHEDRON LETTERS

Heterocyclization of 4-Trifluoroacetyl-2,3-dihydropyrroles with Hydrazines and Amidines: A New Access to Trifluoromethylated Pyrazoles and Pyrimidines Bearing a β-Aminoethyl Side Chain

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Received 4 December 1998; revised 11 January 1999; accepted 22 January 1999

Abstract: Trifluoromethyl-substituted heterocycles have been prepared by condensation of the new 4-trifluoroacetyl-2,3-dihydropyrroles with hydrazines or amidines as a bifunctional *N*-nucleophile with opening of the dihydropyrrole ring.

We have recently reported that the reaction of *N*-alkoxycarbonylprolines (**1**) with trifluoroacetic anhydride (TFAA) provides a convenient route to 4-trifluoroacetyl-2,3-dihydropyrroles (**2**).[1] In view of the versatility of its enaminone (N-C=C-C=O) pattern in synthetic chemistry,[2] we envisioned the use of **2** as useful synthons for CF_3-substituted heterocycles, which have received considerable attention because of their importance in medicinal and agricultural scientific fields.[3] Although there are a few reports dealing with β-enamino trifluoromethylketones,[4] the use of cyclic enaminone of type **2** in the synthesis of heterocycles has not been reported. We found that the compound (**2**) was a new 1,3-ambident electrophile reacting with bifunctional *N*-nucleophiles such as hydrazines and amidines to give CF_3-substituted pyrazoles and pyrimidines bearing a β-aminoethyl side chain. The whole reaction sequence represents a special type of ring transformation by ring-chain-transfer where a ring and a chain moiety in the educt are transferred to each other, giving the product.[5] In view of the pharmacological interest in heterocycles bearing both CF_3 appendage[3] and a β-aminoethyl side chain,[6] the method is very attractive.

Thus, treatment of **2** with 3 equiv. of phenylhydrazine·HCl in EtOH under reflux for 24 h afforded the 3-trifluoromethyl-4-(2-aminoethyl)pyrazole (**3a**) in 92% yield (Table 1, entry 3). It was found that the hydrochloride salt is necessary for this reaction. Attempts to conduct the reaction with the free base gave only the non-cyclized **5**, which was formed by the addition of phenylhydrazine to trifluoromethyl ketone (Entry 1). The reaction under basic conditions led to a complex mixture due to the decomposition of **2** (Entry 2). The formation of this regioisomer (**3a**) can be explained by the primary attack of the more nucleophilic amino group of phenylhydrazine at the trifluoroacetyl group to give **5**, which could be dehydrated by the *in situ*-generated HCl to lead to intermediate (**A**). The ring closure of **A** could occur in a 5-*exo*-*trig* manner[7] to afford **B**, which is converted to **3a**. Under similar conditions, hydrazine·HCl yielded the corresponding pyrazole **3b** (93%)(Entry 5). The reaction with hydrazine hydrate resulted in a lower yield of **3b** (Entry 4). In the case of methylhydrazine, its hydrochloride salt was not commercially available. We thus devised the addition of pyridine hydrochloride to allow the smooth reaction of **2** with methylhydrazine, and the regioisomeric

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PII: S0040-4039(99)00197-5

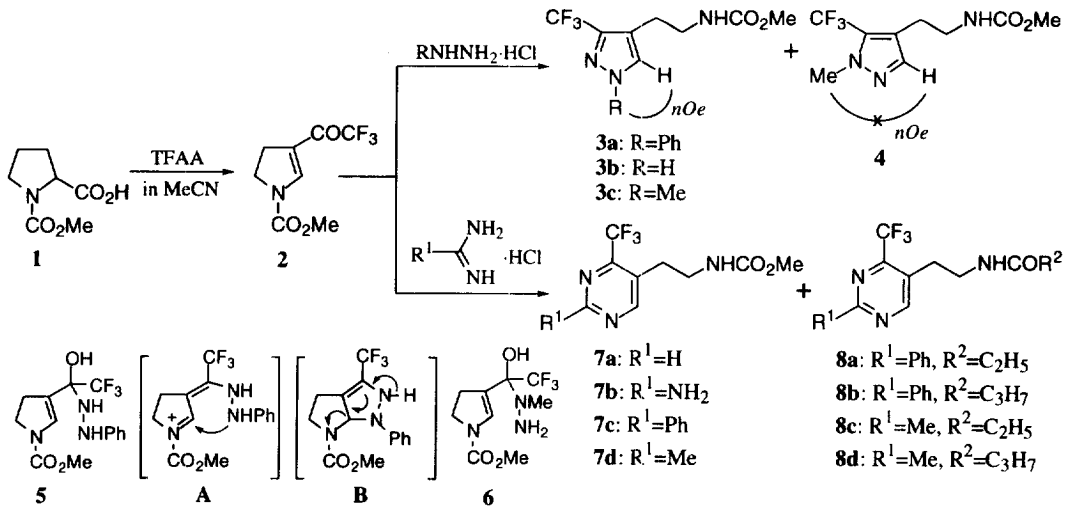


Table 1. Trifluoromethylated pyrazoles from compound **2** and hydrazines

Entry	Hydrazine (Equiv.)[a]	Additive (Equiv.)[a]	Solvent	Reaction condition	Product (Yield, %)[b]
1	$PhNHNH_2$ (3)	---	EtOH	reflux, 4h	**5** (60)
2	$PhNHNH_2$ (3)	NaH (3)	Benzene	r.t., 4h	---[c]
3	$PhNHNH_2$•HCl (3)	---	EtOH	reflux, 24h	**3a** (92)
4	NH_2NH_2•H_2O (3)	---	EtOH	reflux, 3h	**3b** (60)
5	NH_2NH_2•HCl (3)	---	EtOH	reflux, 24h	**3b** (93)
6	$MeNHNH_2$ (3)	---	EtOH	reflux, 7h	**6** (89)
7	$MeNHNH_2$ (3)	Pyridine•HCl (3)	EtOH	reflux, 24h	**3c** (52) + **4** (31)
8	$MeNHNH_2$ (3)	Pyridine•HCl (3)[d]	EtOH	reflux, 24h	**3c** (4) + **4** (91)

[a] Equiv. refers to molar equivalents with respect to **2**. [b] Isolated yields of pure products.
[c] Complex mixture. [d] After a solution of **2** and methylhydrazine in abs. EtOH was refluxed for 7 h, pyridine •HCl was added to the reaction mixture.

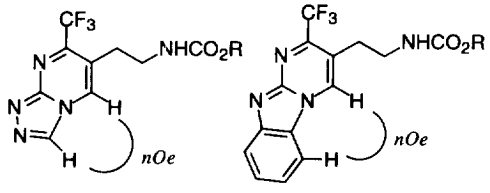
pyrazoles **3c** (52%) and **4** (31%) were isolated (Entry 7). Again, the reaction with the free base afforded only the non-cyclized **6** in 89% yield (Entry 6). The regioselectivity is highly improved by the procedure described in entry 8 of Table 1. Thus, the regioselective formation of **4** could be determined at the stage of an attack at the trifluoroacetyl group by the substituted nitrogen (*N*-1) of methylhydrazine.

Next, the reactions of **2** with 1,3-bifunctional *N*-nucleophiles, such as amidines and guanidine, were carried out under various reaction conditions. The results are summarized in Table 2. The reaction of **2** with formamidine·HCl (3 mol equiv.) in refluxing EtOH for 86h gave a moderate yield of **7a** (51%)(Table 2, entry 1). The reaction temperature also has a profound effect on the outcome of this reaction. The reaction at higher temperature (in hexanol at 185 ℃, 8 h) provided a 74% yield of **7a** (Entry 3). Under similar conditions, three hydrochloride salts of acetamidine, benzamidine, and guanidine afforded the corresponding

Table 2. 4-Trifluoromethylpyrimidines from compound **2** and amidines

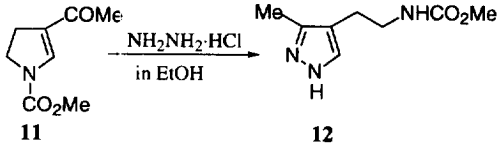
Entry	Amidine R^1	Solvent	Reaction condition	Product (Yield, %)[a]
1	H	EtOH	reflux 86h	**7a** (51)
2	H	AcOH	reflux 40h	**7a** (25)[b]
3	H	Hexanol	reflux 8h	**7a** (74)
4	NH_2	Hexanol	reflux 24h	**7b** (44)
5	Ph	Hexanol	reflux 15h	**7c** (18)
6	Ph	Propionic acid	reflux 28h	**7c** (29) + **8a** (10)
7	Ph	Butyric acid	reflux 20h	**7c** (6) + **8b** (53)
8	Me	Hexanol	reflux 7h	**7d** (23)
9	Me	Propionic acid	reflux 32h	**7d** (21) + **8c** (27)
10	Me	Butyric acid	reflux 24h	**7d** (3) + **8d** (36)

[a] Isolated yields of pure products. [b] The starting **2** was recovered in 40% yield.



9a: R=Me (y. 82%)
9b: R=C_6H_{13} (y. 6%)

10a: R=Me (y. 35%)
10b: R=C_6H_{13} (y. 34%)



11 **12**

pyrimidines **7d**, **7c**, and **7b** in 23%, 18%, and 44% yields, respectively (Entries 8, 5, and 4). The use of an aprotic solvent such as DMF, DMSO, and xylene did not give any characterized product, but led to complete destruction of **2**. In order to increase the yield, other protic solvents were examined. The reaction of **2** with benzamidine·HCl in butyric acid at 180 ℃ for 20h gave the pyrimidine derivatives **7c** and **8b** in 6% and 53% yields, respectively (Entry 7). The reaction with acetamidine·HCl in propionic acid at 170 ℃ for 32h afforded the pyrimidine derivatives **7d** and **8c** in 21% and 27% yields, respectively (Entry 9). Compounds (**8a-d**) were formed by the replacement of the methoxycarbonyl group with the acyl group, derived from the solvent carboxylic acid. Both prolonged reaction time and a high temperature (170-180 ℃) facilitated the exchange of *N*-acyl group.

To extend the scope of this methodology, we examined the reaction with cyclic amidines such as 3-amino-1,2,4-triazole and 2-aminobenzimidazole. Both nucleophiles were used as the free base and reacted with **2** in refluxing hexanol to yield the condensed products (**9a,b** and **10a,b**) in good yields, respectively. The production of **9b** and **10b** is due to the exchange of the methoxy group with the hexyloxy group, derived from the solvent hexanol.

In order to confirm the necessity for the presence of the trifluoroacetyl group of **2** on the effectiveness of this reaction, the comparison with non-fluorinated **11** is interesting. Thus, 4-acetyl-2,3-dihydropyrrole (**11**), prepared by the literature method,[8] similarly reacts with hydrazine·HCl to yield the corresponding pyrazole (**12**) in 69% yield.

The structure determination of products (**3-10** and **12**) was performed by spectral data.[9] The structures of

3, **4**, **9** and **10** were assigned by ^{1}H NMR measurement on the basis of the observed NOE.[10]

In summary, the reaction can serve as a convenient route to CF_3-substituted pyrazole and pyrimidine derivatives bearing a β-aminoethyl side chain. The ring transformation in this series was termed "ring-chain transformation" due to the fact that the starting ring becomes a chain in the product.[5] Especially, this synthesis offers various heterocyclic analogs of biologically active histamine and dopamine. It is reported that the pyrazole ring system can function as bioisostere of the dopamine catechol nucleus.[11] Recently, we have reported that dopamine analogs show interesting biological activities such as apoptosis-induced cytotoxic activity, anti-multidrug resistance on tumor cells, and so on.[12] Further synthetic utility of the 4-trifluoroacetyl-2,3-dihydropyrrole (**2**) for the synthesis of biologically important heterocycles is under investigation.

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9. All new compounds gave satisfactory analytical and spectral data. Selected data for representative heterocycles prepared in this work: **3b**: mp 100-102 ℃ (AcOEt-hexane), δ_H ($CDCl_3$) 2.75 (t, 2H, *J*=7.0 Hz), 3.27-3.31 (m, 2H), 3.62 (s, 3H), 6.63 (s, 1H, NH), 7.52 (s, 1H), 13.05 (br s, 1H, NH); δ_C ($CDCl_3$) 22.56 (CH_2), 40.07 (CH_2), 50.47 (CH_3), 115.08 (C), 121.26 (CF_3, $^1J_{CF}$=269.0 Hz), 127.97 (CH), 139.05 (C), 156.11 (C). **7a**: oil, δ_H ($CDCl_3$) 3.01 (t, 2H, *J*=6.7 Hz), 3.40-3.44 (m, 2H), 3.61 (s, 3H), 5.03 (br s, 1H, NH), 8.80 (s, 1H), 9.18 (s, 1H); δ_C ($CDCl_3$) 29.47 (CH_2), 41.15 (CH_2), 52.26 (CH_3), 121.09 (CF_3, $^1J_{CF}$=276.2 Hz), 129.98 (C), 153.04 (C, $^2J_{CF}$=35.2 Hz), 156.71 (C), 157.00 (CH), 161.36 (CH).
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