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Regioselective Reaction of Mesoionic 4-Trifluoroacetyl-1,3-oxazolium-5-olates and Phenylhydrazine: Synthesis of Trifluoromethyl Substituted Pyrazole and 1,2,4-Triazine Derivatives

Masami Kawase,[*a] **Hiromi Koiwai,**[a] **Akihito Yamano**[b] **and Hiroshi Miyamae**[c]

[a] *Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-02, Japan*

[b] *Rigaku Corporation, 3-9-12 Matsubara, Akishima, Tokyo 196, Japan*

[c] *Faculty of Science, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-02, Japan*

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Abstract: 6-Trifluoromethyl-1,2,4-triazines (**2**), 3-trifluoromethyl-5-pyrazolones (**3**), or 5-trifluoromethyl-3-hydroxypyrazoles (**4**) are selectively obtained in good yields through the regioselective attack of phenylhydrazine on mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**), depending on the nature of the reaction solvent and temperature.

We have recently reported that mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) are useful synthons for the synthesis of trifluoromethyl substituted imidazoles by the reaction with amidines[1] or ammonia.[2] These reactions occur *via* initial attack of the nucleophiles on the C-2 position of the ring. In line with our continuing interest, we have undertaken investigation of the reaction of **1** with a bis-nucleophile such as phenylhydrazine (PH). In principle, nucleophilic reagents can be expected to add to one of the three electrophilic centers at C-2, C-5, and $COCF_3$ in **1**. This paper is devoted to the behaviour of **1** with PH from the chemo- and regioselectivity point of view; herein, efficient syntheses of new fluorinated heterocycles in the 1,2,4-triazine (**2**), 5-pyrazolone (**3**), and pyrazole (**4**) series are reported.

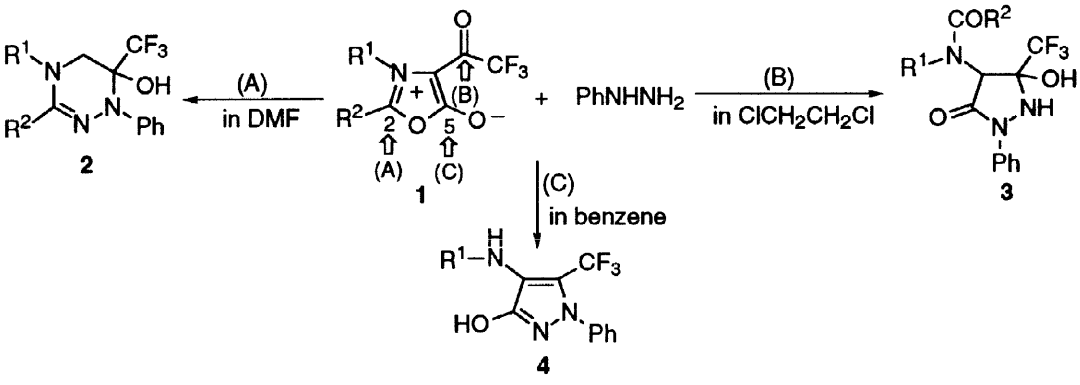

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Table 1. Reactions of compounds **1a-e** and phenylhydrazine

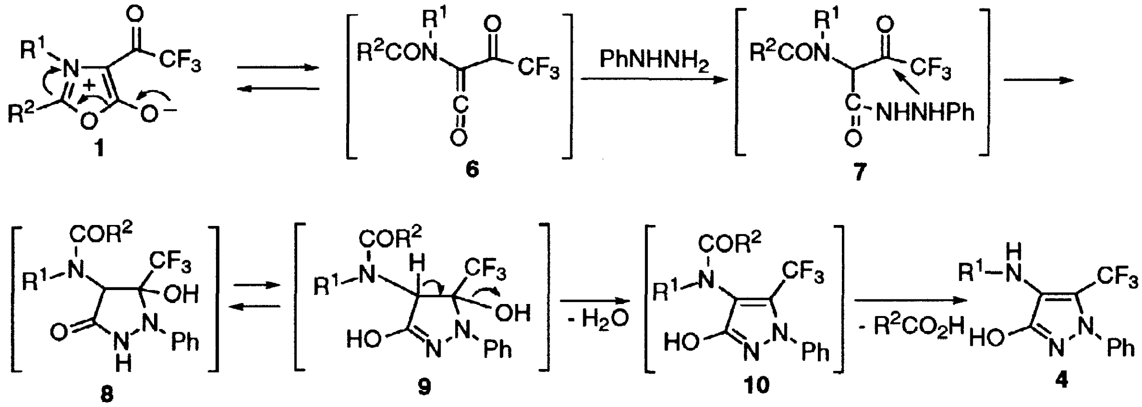
Starting compound			Reaction conditions	Product			
1	R^1	R^2			R^1	R^2	Yield (%)
a	Me	Ph	$PhNHNH_2$ in DMF rt for 24 h	**2a**	Me	Ph	74
b	Me	$4\text{-}MeOC_6H_4$		**2b**	Me	$4\text{-}MeOC_6H_4$	40
c	Me	$4\text{-}BrC_6H_4$		**2c**	Me	$4\text{-}BrC_6H_4$	68
d	Bn	$4\text{-}MeOC_6H_4$		**2d**	Bn	$4\text{-}MeOC_6H_4$	64
e	Ph	$4\text{-}MeOC_6H_4$		**2e**	Ph	$4\text{-}MeOC_6H_4$	88
a	Me	Ph	$PhNHNH_2$ in DCE rt for 24 h	**3a**[a]	Me	Ph	62
b	Me	$4\text{-}MeOC_6H_4$		**3b**[a]	Me	$4\text{-}MeOC_6H_4$	70
c	Me	$4\text{-}BrC_6H_4$		**3c**[a]	Me	$4\text{-}BrC_6H_4$	48
d	Bn	$4\text{-}MeOC_6H_4$		**3d**[a]	Bn	$4\text{-}MeOC_6H_4$	14[b]
e	Ph	$4\text{-}MeOC_6H_4$		**3e**[a]	Ph	$4\text{-}MeOC_6H_4$	41
a	Me	Ph	$PhNHNH_2$ in benzene reflux for 2 h	**4a**	Me	-	63
b	Me	$4\text{-}MeOC_6H_4$		**4a**	Me	-	73
c	Me	$4\text{-}BrC_6H_4$		**4a**	Me	-	46
d	Bn	$4\text{-}MeOC_6H_4$		**4b**	Bn	-	95
e	Ph	$4\text{-}MeOC_6H_4$		-	-	-	-[c]

[a] The single isomer was isolated. The stereochemistry of **3** has not yet been determined.
[b] Plus **4b** (y. 55%). [c] Compounds **5** and **3e** were isolated in 24% and 25% yields, respectively.


$R{=}4\text{-}MeOC_6H_4$
5

First, compounds **1a-e** were treated in DMF at room temperature with PH (1.5 mol equiv.); a smooth reaction took place and the 6-trifluoromethyl-1,2,4-triazines (**2a-e**) were obtained in good yields (Table 1). The reaction appears to proceed *via* a similar mechanism to that described in the reaction of **1** and NH_3.[1] In general, the terminal nitrogen (N-2) of PH is more nucleophilic than the substituted nitrogen (N-1) in neutral media.[3] Thus, the first step of the reaction consists apparently of an attack at C-2 by the terminal nitrogen (N-2) of PH, and finally, the internal attack at the trifluoromethyl ketone by the substituted nitrogen (N-1) of PH moiety leads to **2** through the ring opening-ring closure sequence. Second, the same reaction was carried out in a 1,2-dichloroethane (DCE) solution, instead of DMF; the products were 3-trifluoromethyl-5-pyrazolones (**3**). None of the 1,2,4-triazine derivative was formed in the reaction. Thus, the trifluoromethyl ketone was at first attacked by PH and the reaction proceeded by a ring closure-ring opening sequence. Third, the reaction of **1** with PH in refluxing benzene solution afforded 5-trifluoromethyl-3-hydroxypyrazoles (**4**) in good yields. At the elevated temperature, the ring of **1** opens to give trifluoroacetylketenes (**6**). Then, PH attacked at the ketene carbonyl of **6**, subsequently at the trifluoromethyl ketone. In this case, the possible intermediates (**8** or **9**) were not isolated, thus showing that dehydration of **9** followed by hydrolysis of the resulting amide (**10**) to **4** occurred easily under the adopted reaction conditions (Scheme 1). The driving force of the dehydration is probably due to stabilization by the formation of an aromatic pyrazole derivative.[4]

The reason why the reaction affords a completely different product depending on the reaction solvent and temperature is still unclear. However, the reaction medium and reaction temperature play an important role in



Scheme 1

directing the regiochemistry. It is possible that with DMF as solvent, the highly polar, mesoionic form of **1** is stabilized. This leads to the mode of attack by PH at C-2 of **1**, leading to the products (**2**). In contrast, it is also likely that in the less polar solvents, the mesoionic **1** is in equilibium with the trifluoroacetylketene (**6**). The process would be facilitated by the elevated temperature of refluxing benzene. Similar ketene-type valence tautomers are often encountered in the cycloadditions of these mesoionic systems.[5]

The structure determinations of products **2**, **3**, and **4** were performed by spectral data.[6] The structure of **4a** was unequivocally confirmed by the X-ray analysis (Figure 1).[7] Benzoylation of **4a** with benzoyl chloride in the presence of pyridine afforded **11** in 87% yield. When treated with benzoic anhydride in the presence of pyridine under reflux in benzene, **3a** underwent dehydration and benzoylation in 59% yield to give **12** which was the regioisomer of **11**. Accordingly, these transformations confirmed the structure of **3a**. The regioisomeric pyrazoles **11** and **12** have significantly different ^{13}C NMR spectra as shown in Figure 2.[8]

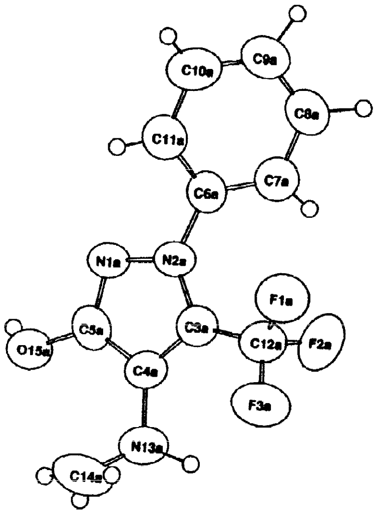


Figure 1. X-ray structure drawing of 4a

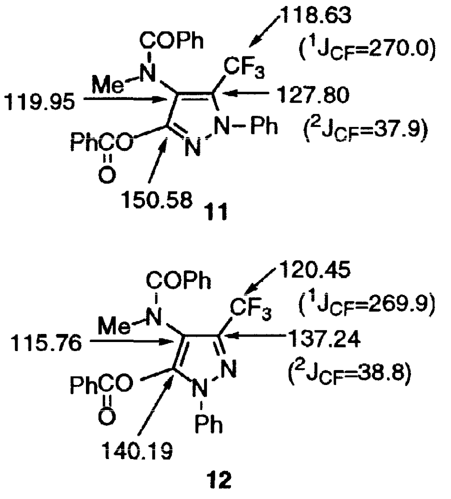


Figure 2

Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**), readily available from *N*-alkyl-*N*-acylglycines and trifluoroacetic anhydride, reacted with PH giving either 6-trifluoromethyl-1,4,5,6-tetrahydro-6-hydroxy-1,2,4-triazines (**2**), 3-trifluoromethyl-5-pyrazolones (**3**), or 5-trifluoromethyl-3-hydroxypyrazoles (**4**), depending on the solvent polarity and reaction temperature. By proper choice of these parameters the trifluoromethylated heterocycles could be selectively obtained in good yields. In addition, the method appears to be useful and convenient in terms of the ready accessibility of the starting materials, cheap reagents, and operational simplicity. In contrast to trifluoromethylated pyrazoles,[9] 1,2,4-triazines which have trifluoromethyl groups seem to be less known in the literature, although some trifluoromethylated 1,2,4-triazines were developed as agrochemicals.[10] Further synthetic utility of **1** for the synthesis of other fluorinated heterocycles is under investigation.

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6 Selected data for representative heterocycles prepared in this work: **2a**: δ_H ($CDCl_3$) 2.88 (s, 3H), 3.48 (dq, 1H, J=2.1, 12.8), 3.73 (dq, 1H, J=2.1, 12.8), 7.13-7.18 (m, 1H), 7.27-7.32 (m, 2H), 7.36-7.39 (m, 4H), 7.40-7.44 (m, 1H), 7.48-7.51 (m, 2H); δ_C ($CDCl_3$) 40.47 (CH_3), 52.41 (CH_2), 79.27 (C, $^2J_{CF}$=30.0), 123.49 (CF_3, $^1J_{CF}$=290.7), 125.56(CH), 125.69 (CH), 128.32 (CH), 128.57 (CH), 128.71 (CH), 129.16 (CH), 133.82 (C), 144.58 (C), 147.11 (C). **3a**: δ_H 3.21 (s, 3H), 4.28-4.48 (br, 1H, D_2O changeable), 5.16 (s, 1H, D_2O changeable), 7.19 (t, 1H, J=7.6), 7.36 (t, 2H, J=7.6), 7.44 (t, 2H, J=7.6), 7.50 (t, 1H, J=7.6), 7.58 (d, 2H, J-7.6), 7.76 (d, 2H, J=7.6); δ_C 41.10 (CH_3), 65.00 (CH), 86.73 (C, $^2J_{CF}$=32.0), 118.92 (CH), 122.68 (CF_3, $^1J_{CF}$=283.5), 125.70 (CH), 127.78 (CH), 128.60 (CH), 128.92 (CH), 131.26 (CH), 133.32 (C), 137.08 (C), 161.10 (CO), 176.20 (CO). **4a**: δ_H 2.86 (s, 3H), 7.34-7.41 (m, 3H), 7.42-7.46 (m, 2H); δ_C 34.91 (CH_3), 119.38 (C, $^2J_{CF}$=37.6), 120.45 (CF_3, $^1J_{CF}$=260.0), 121.93(C), 125.33 (CH), 128.37 (CH), 129.09 (CH), 139.05 (C), 154.79 (CO).

7. Crystal data for **4a** ($C_{11}H_{10}N_3OF_3$) FW=257.21, mp 117-119 °C (cyclohexane). Triclinic $P\bar{1}$. a=10.488(5), b=13.754(10), c=9.478(2)Å, α=107.81(3), β=108.38(4), γ=103.26(6)°, V=1154.3(13) $Å^3$, μ(MoKα)=1.244 cm^{-1} by Rigaku RAXIS II. Final R value was 0.078 for 2333 independent reflections with I≥3σ(I)(R_W=0.025, S=8.451). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
8. ^{13}C NMR chemical shifts of 3-trifluoromethyl-5-hydroxy- and 5-trifluoromethyl-3-hydroxypyrazoles are described in the following literature: Lee, L. F.; Schleppnik, F. M.; Schneider, R. W.; Campbell, D. H. *J. Heterocyclic Chem.*, **1990**, 27, 243.
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