ELSEVIER

Journal of Fluorine Chemistry 120 (2003) 29–32

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Cyclocondensation reaction of 4-aryl-4-methoxy-1,1,1-trifluoro-3-buten-2-ones with urea Synthesis of novel 6-aryl(5-methyl)-4-trifluoromethyl-2(1*H*)-pyrimidinones

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Received 23 September 2002; received in revised form 14 October 2002; accepted 25 October 2002

Abstract

The synthesis of a novel series of eleven 6-aryl(5-methyl)-4-trifluoromethyl-2(1*H*)-pyrimidinones, where aryl = Ph, 4-CH_3Ph, 4-FPh, 4-ClPh, 4-BrPh, 4-OCH_3Ph and alkyl = H, CH_3, from the reaction of 4-aryl-4-methoxy-1,1,1-trifluoro-3-buten-2-ones with urea in the presence of hydrochloric acid, is reported. Trifluoroacetylation of acetophenone- and propiophenone-dimethylacetals derived from phenones, was employed to obtain the precursors.
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Keywords: 2(1*H*)-pyrimidinones; Pyrimidines; Enones; Cyclization

1. Introduction

Introduction of a trifluoromethyl group and higher homologue C_nF_{2n+1} substituents into a heterocycle frequently results in compounds, which display more potent activity than the parent, a fact which is probably due to the lipophylicity of the perfluoroalkyl substituents [1,2]. One of the better methods to introduce a trifluoromethyl group into heterocycles is based on the trifluoromethylated building block approach. This approach relies on the trifluoroacetylation of enolethers or acetals to give, in one step and good yield, β-alkoxyvinyl trifluoromethyl ketones which proved to be useful building blocks for the synthesis of five- [3–5], six- [6,7], and seven-membered [8] heterocyclic compounds. Recently, β-ethoxyvinyltrifluoromethyl ketone and cycloanalogues, as building block to construct fluorine containing heterocycles, have been widely studied and reviewed [9].

As an extension of these works we are now investigating the possibility to obtain 6-aryl substituted and 6-aryl-5-methyl substituted 2(1*H*)-pyrimidinones using the trifluoromethylated building block approach.

Only a few literature reference's report the synthesis of non-fluorinated phenyl- and alkyl-substituted 2(1*H*)-pyrimidinones, via direct cyclization of 1,3-dicarbonyl derivatives with urea [10,11]. Usually the synthesis of uracils involves a multi-step strategy. One of these methods, involves the condensation of β-ketoesters with thiourea or alkylisothioureas [12–14] and subsequent removal of the S atom [15,16]. Another indirect method to obtain 2(1*H*)-pyrimidinones is the condensation of β-ketoesters with *O*-methylisourea bisulfate, followed by the hydrolysis of the 2-methoxypyrimidin-4-one to the corresponding uracils [17].

A direct and convenient one-pot synthesis of a series of 4-trifluoro[trichloro]methyl-2(1*H*)-pyrimidinones which relies on the cyclocondensation of trifluoroacetylated enol ethers (vinyl-, propenyl- and isopropenyl-alkyl ethers) or isobutyl methyl dimethylacetals and urea was developed in our research group [18,19]. This approach allowed only the synthesis of 5-methyl-, 6-methyl- or 6-isobutyl-4-trifluoromethyl-2(1*H*)-pyrimidinones [18,19]. However, the introduction of a *p*-substituted phenyl as well as a phenyl and a methyl substituent in the 6- and 5-position of the 4-trifluoro-2(1*H*)-pyrimidinone ring, has not yet been reported. In 1996, C-M. Hu et al. reported the synthesis of 2-substituted 6-fluoroalkyl-4-(3*H*)-pyrimidinones, in excellent yields, by treatment of α-fluoroalkylacetates or ethyl 3-fluoroalkyl-2-iodoacrylates

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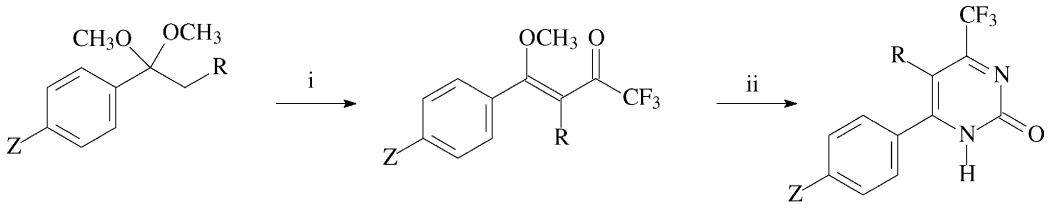
PII: S0022-1139(02)00287-7



1a-k **2a-k** **3a-k**

i. $(CF_3CO)_2O$, pyridine, $CHCl_3$, 0 - 60 °C, 16 - 24 h (52 - 91 %)
ii. $(NH_2)_2CO$, MeOH, HCl conc., 24 - 72 h, reflux, (23 - 52%)

1-3	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**
Z	H	CH_3	F	Cl	Br	OMe	H	Me	Cl	Br	OMe
R	H	H	H	H	H	H	Me	Me	Me	Me	Me

Scheme 1. Preparation of 2(1*H*)-pyrimidinones via trifluoroacetylation of phenones dimethylacetals.

with benzamidine and acetamidine [20]. However, attempts to extend this reaction with thiourea and urea as reagent in place of amidines failed even when potassium hydroxide or sodium hydride was used as base [20]. This situation prompted us to investigate and report the synthesis of 6-aryl and 5-methyl-6-aryl-substituted trifluoromethylated 2(1*H*)-pyrimidinones **3** from the reaction between β-methoxyvinyl trifluoromethyl ketones **2** obtained from the trifluoroacetylation of phenones dimethylacetals **1** and urea (Scheme 1).

2. Results and discussion

The best reaction conditions, selected physical and spectral data are presented in the experimental part and in Tables 1–3, respectively. The β-methoxyvinyl trifluoromethyl ketones **2a–k** were prepared according to [21,22].

The cyclocondensation reactions of compounds **2a–k** with urea were carried out in methanol in the presence of hydrochloric acid. The reactions were monitored by TLC and the optimal reaction time and temperature were 24 h at 60–65 °C (reflux) for **3a–f** and 72 h at same temperature for **3g–k**. The yields of the cyclization reactions depended on the structure of the precursor **2a–k**. The ^{1}H NMR spectra showed compounds **2g–k** as a mixture of *Z* and *E* configuration in 2:1 ratio while compounds **2a–f** exhibited almost only *E* configuration [22]. These observations suggest that the conformation of **2a–k** is the main factor to explain the yields of these reactions. Considering the similar reaction conditions for the synthesis of 2(1*H*)-pyrimidinones **3a–k**, the difference of the observed yields could be related with the activation energy required to achieve planarity of the enone functionality in **2a–k**. There is a significant difference in energy among the molecules of the series **2a–f** and **2g–k** for the fundamental state and the transition state (planar structure). We performed MO calculation carried out by the Austin Model 1 (AM1) semiempirical method [23,24] in order to have a better understanding of the initial conformation and activation energy and consequently the reactivity of

Table 1
Selected physical and mass spectral data of trifluoromethylated 2(1*H*)-pyrimidinones **3a–k**

Compounds	*Z*	R	Yield (%)[a]	mp (°C)[b]	MS [*m*/*z* (%)]
3a	H	H	50	233–235	240 (M^+, 100), 212 (33), 171 (9), 69 (8)
3b	CH_3	H	51	253–255	254 (M^+, 100), 226 (11), 185 (7), 69 (4)
3c	F	H	50	>300	258 (M^+, 100), 230 (20), 189 (7), 69 (10)
3d	Cl	H	48	207–209	274 (M^+, 100), 246 (16), 205 (7), 69 (9)
3e	Br	H	50	200–202	318 (M^+, 56), 299 (15), 249 (5), 69 (12)
3f	OCH_3	H	52	244–246	270 (M^+,100), 249 (13), 201 (4), 69 (10)
3g	H	CH_3	24	250–252	253 (M^+, 100), 235 (7), 184 (4), 69 (3)
3h	CH_3	CH_3	28	221–223	267 (M^+, 89), 198 (4) 69 (4)
3i	Cl	CH_3	23	218–220	287 (M^+, 100), 253 (20), 217 (1), 69 (5)
3j	Br	CH_3	24	206–207	333 (M^+, 100), 283 (43), 265 (4), 69 (8)
3k	OCH_3	CH_3	25	210–211	283 (M^+, 100), 253 (16), 214 (2), 69 (3)

[a] Yield of isolated compounds.
[b] Melting points determined with a Reichert Thermovar apparatus and are uncorrected.

Table 2
Elemental analyses data of trifluoromethylated 2(1*H*)-pyrimidinones **3a–k**

Compounds	Molecular formula weight (g/mol)	Elemental analysis (%)					
		Calculated			Found		
		C	H	N	C	H	N
3a	$C_{11}H_7ON_2F_3$ (240.18)	55.01	2.94	11.66	55.15	3.19	11.55
3b	$C_{12}H_9ON_2F_3$ (254.21)	56.70	3.57	11.02	56.79	3.76	10.92
3c	$C_{11}H_6ON_2F_4$ (258.17)	51.17	2.34	10.85	51.16	2.67	10.34
3d	$C_{11}H_6ON_2F_3Cl$ (274.62)	48.11	2.20	10.20	48.08	2.47	9.88
3e	$C_{11}H_6ON_2F_3Br$ (319.08)	41.14	1.90	8.78	41.57	2.17	8.56
3f	$C_{12}H_9O_2N_2F_3$ (270.21)	53.34	3.36	10.37	52.97	3.17	10.05
3g	$C_{12}H_9ON_2F_3$ (254.21)	56.70	3.57	11.02	56.80	3.70	10.81
3h	$C_{13}H_{11}ON_2F_3$ (268.23)	58.21	4.13	10.44	58.31	4.21	10.26
3I	$C_{12}H_8ON_2F_3Cl$ (288.65)	49.93	2.79	9.70	49.70	2.51	9.43
3j	$C_{12}H_8ON_2F_3Br$ (333.10)	43.27	2.42	8.41	43.12	2.54	8.17
3k	$C_{13}H_{11}O_2N_2F_3$ (284.23)	54.93	3.90	9.86	54.58	3.99	9.78

these compounds. From the MO calculation was observed that the methyl substituent at the 3-position of **2g–k** does not favor the formation of the 2(1*H*)-pyrimidinones **3g–k**. The steric hindrance of the substituents attached to C-3 and C-4 of **2g–k** takes the carbonyl and the olefinic double bond out of the planarity. For example, the AM1 calculations showed that **2g** (propiophenone derivative) requires an activation energy of 3.88 kcal/mol (*Z* isomer) and 9.09 kcal/mol (*E* isomer) to establish a planar conformation while for **2a** (acetophenone derivative) only 0.1 kcal/mol is sufficient. This indicate, that the attack of the urea nitrogen to C-4 might be more difficult, resulting in a low yield for compounds **3g–k**. On the other hand, the compounds derived from acetophenones **2a–f** allow the isolation of 2(1*H*)-pyrimidinones **3a–f** in satisfactory yield (48–52%).

We consider the presented one-pot reaction to be a useful and convenient alternative to obtain 6-aryl- and 6-aryl-5-methyl-4-trifluoromethyl-2(1*H*)-pyrimidinones **3**. In summary,

Table 3
NMR spectral data of trifluoromethylated 2(1*H*)-pyrimidinones (**3a–k**) in DMSO-d_6 and TMS as internal reference

Compounds	^{1}H NMR, δ/^{13}C NMR, δ, J_{C-F} (Hz)
3a	12.9 (s, 1H, NH), 8.2–7.6 (m, 5H, H-Ar), 7.8 (s, 1H, H-5) 167.1 (C-6), 163.6 (C-2), 158.1 (q, J = 31, C-4), 134.0, 132.2, 129.0, 128.0, (6C, Ar), 120.5 (q, J = 274, CF_3), 103.2 (C-5)
3b	12.8 (s, 1H, NH), 8.1–7.3 (m, 4H, H-Ar), 7.7 (s, 1H, H-5), 2.4 (s, 3H, CH_3) 166.7 (C-6), 163.2 (C-2), 158.2 (q, J = 29, C-4), 142.5, 130.9, 129.5, 127.5 (6C, Ar), 120.4 (q, J = 274, CF_3), 102.5 (C-5), 20.9 (*p*-CH_3)
3c	12.9 (s, 1H, NH), 8.3–7.3 (4H, H-Ar), 7.8 (s, 1H, H-5) 166.4 (C-6), 164.0 (C-2), 157.9 (q, J = 33, C-4), 164.9, 130.7, 130.3, 116.0, (6C, Ar), 120.5 (q, J = 274, CF_3), 103.7 (C-5)
3d	12.9 (s, 1H, NH), 8.2–7.5 (m, 4H, H-Ar), 7.8 (s, 1H, H-5) 166.5 (C-6), 164.3 (C-2), 157.9 (q, J = 34, C-4), 137.4, 133.1, 129.7, 129.0 (6C, Ar), 120.5 (q, J = 274, CF_3), 104.0 (C-5)
3e	12.9 (s, 1H, NH), 8.1–7.7 (m, 4H, H-Ar), 7.9 (s, 1H, H-5) 166.6 (C-6), 164.3 (C-2), 157.8 (q, J = 34, C-4), 133.5, 131.9, 129.5, 126.0 (6C, Ar), 123.1 (q, J = 274, CF_3), 104.0 (C-5)
3f	12.7 (s, 1H, NH), 8.1–7.0 (m, 4H, H-Ar), 7.6 (s, 1H, H-5), 3.8 (s, 3H, *p*-OCH_3) 166.6 (C-6), 163.0 (C-2), 158.0 (q, J = 34, C-4), 166.6, 131.9, 129.5, 126.0 (6C-Ar), 120.5 (q, J = 275, CF_3), 101.7 (C-5)
3g	12.6 (s, 1H, NH), 7.5 (s, 5H, H-Ar), 2.1 (s, 3H, CH_3) 167.0 (C-6), 159.5 (C-2), 157.0 (q, J = 33, C-4), 134.6, 130.0, 128.7, 128.5 (6C, Ar), 121.0 (q, J = 276, CF_3), 112.7 (C-5), 12.6 (CH_3)
3h	12.5 (s, 1H, NH), 7.4–7.3 (m, 4H, H-Ar), 2.4 (s, 3H, *p*-CH_3), 2.1 (s, 3H, CH_3) 166.7 (C-6), 159.1 (C-2), 157.0 (q, J = 32, C-4), 139.8, 131.5, 128.8 (6C, Ar), 120.9 (q, J = 276, CF_3), 112.2 (C-5), 20.7 (*p*-CH_3), 12.5 (CH_3)
3i	12.5 (s, 1H, NH), 7.4–7.0 (m, 4H, H-Ar), 3.4 (s, 3H, CH_3) 168.6 (C-6), 166.2 (C-2), 154.5 (q, J = 30, C-4), 138.3, 133.0, 130.6, 127.9, (6C-Ar), 122.0 (q, J = 276, CF_3), 105.2 (C-5), 12.9 (CH_3)
3j	12.6 (s, 1H, NH), 7.8–7.5 (m, 4H, H-Ar), 2.1 (s, 3H, CH_3) 166.8 (C-6), 160.2 (C-2), 156.6 (q, J = 34, C-4), 134.2, 131.4, 131.1, 123.7 (6C, Ar), 121.0 (q, J = 276, CF_3), 113.8 (C-5), 12.8 (CH_3)
3k	12.5 (s, 1H, NH), 7.5-7.0 (m, 4H, H-Ar), 3.8 (s, 3H, *p*-OCH_3), 2.0 (s, 3H, CH_3) 166.1 (C-6), 159.0 (C-2), 157.1 (q, J = 32, C-4), 160.6, 130.7, 126.3, 113.7 (6C, Ar), 120.9 (q, J = 276, CF_3), 111.9 (C-5), 55.2 (*p*-OCH_3), 12.6 (CH_3)

the use of this methodology allowed the isolation of a new series of 4-trifluoromethylated 2(1*H*)-pyrimidinones **3** which have been prepared in analytically pure form and in relative satisfactory yield.

3. Experimental

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6 and using TMS as internal reference. Mass spectra were registered in a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. The CHN elemental analysis were performed on a Perkin-Elmer 2400 CHN elemental analyser (São Paulo University—USP/Brazil).

3.1. Synthesis of 6-aryl(5-methyl)-4-trifluoromethyl-2(1H)-pyrimidinones 3

3.1.1. General procedure

To a magnetically stirred solution of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **2a–k** (5 mmol) and urea (0.6 g, 10 mmol) in 10 ml of methanol at 20–25 °C was added 1 ml of concentrated HCl. The mixture was refluxed at 60–65 °C for 24 h (**2a–f**) or for 72 h (**2g–k**). Distilled water (15 ml) was added to the reaction mixture's at room temperature and the products (**3a–k**) were allowed to crystallize by cooling the solutions to 5–8 °C for 12 h. The solids were filtered off, washed with cold water and dried overnight in a dessicator under phosphorus pentoxide at room temperature. The products were recrystallized from dichloromethane: ethanol 1:1 (**3a–f**) or from ethanol 96% (**3g–k**).

Acknowledgements

The authors are thankful for the financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq/PADCT III- Project no. 62.0228/97-0-QEQ).

References

[1] R. Filler, in: R.E Banks (Ed.), Organofluorine Chemicals and Their Industrial Applications, Ellis Horwood, London, 1979.
[2] Y. Inouye, K. Tezuka, W. Takeda, S. Sugai, J. Fluorine Chem. 35 (1987) 275.
[3] H.G. Bonacorso, M.R. Oliveira, A.P. Wentz, A.D. Wastowski, A.B. de Oliveira, M. Hörner, N. Zanatta, M.A.P. Martins, Tetrahedron 55 (1999) 345.
[4] H.G. Bonacorso, A.D. Wastowski, N. Zanatta, M.A.P. Martins, J.A. Naue, J. Fluorine Chem. 92 (1998) 23.
[5] M.A.P. Martins, R. Freitag, A.F.C. Flores, N. Zanatta, Synthesis (1995) 1491.
[6] N. Zanatta, M.B. Fagundes, R. Ellensohn, M. Marques, H.G. Bonacorso, M.A.P. Martins, J. Heterocyclic Chem. 35 (1998) 451.
[7] H.G. Bonacorso, S.R.T. Bittencourt, R.V. Lourega, A.F.C. Flores, N. Zanatta, M.A.P. Martins, Synthesis (2000) 1431.
[8] H.G. Bonacorso, S.R.T. Bittencourt, A.D. Wastowski, A.P. Wentz, N. Zanatta, M.A.P. Martins, Tetrahedron Lett. 37 (1996) 9155.
[9] S.Z. Zhu, Y.L. Wang, W.M. Peng, L.P. Song, G.F. Jin, Curr. Org. Chem. 6 (2002) 1057.
[10] A.R. Katritsky, L.O. Daryl, T.I. Yousaf, Tetrahedron 43 (1987) 5171.
[11] A.R. Katritsky, L.O. Daryl, T.I. Yousaf, Can. J. Chem. 64 (1986) 2087.
[12] S. Senda, A. Suzui, M. Honda, H. Fujimura, K. Maeno, Chem. Pharm. Bull. 6 (1958) 476.
[13] S. Basterfield, F.B.S. Rodman, J.W. Tomecko, E.C. Powell, Can. J. Res. 1 (1929) 285.
[14] R. Hull, B.J. Lovell, H.T. Openshaw, A.R. Todd, J. Chem. Soc. (1947) 41.
[15] F.H.S. Curd, F.L. Rose, J. Chem. Soc. (1946) 343.
[16] R.O. Roblin, J.O. Lampen, J.P. English, Q.P. Cole, J.R. Vaughan, J. Am. Chem. Soc. 67 (1945) 290.
[17] M. Botta, M. Cavalieri, D. Ceci, F. de Angelis, G. Finizia, R. Nicoletti, Tetrahedron 40 (1984) 3313.
[18] I.L. Pacholski, I. Blanco, N. Zanatta, M.A.P. Martins, J. Braz. Chem. Soc. 2 (1991) 118; Chem. Abstract 120 (1994) 323443n.
[19] H.G. Bonacorso, S.R.T. Bittencourt, M.A.P. Martins, R.V. Lourega, N. Zanatta, A.F.C. Flores, J. Fluorine Chem. 99 (1999) 177.
[20] H.-P. Guan, Q.-S. Hu, C.-M. Hu, Synthesis (1996) 997.
[21] M.A.P. Martins, A.F.C. Flores, G.M. Siqueira, R. Freitag, N. Zanatta, Química Nova 17 (1994) 298; Chem. Abstract 121 (1994) 230377z.
[22] M.A.P. Martins, G.M. Siqueira, A.F.C. Flores, G. Clar, N. Zanatta, Química Nova 17 (1994) 24; Chem. Abstract 122 (1995) 187063a.
[23] M.J.S. Dewar, E.G. Zoebisch, E.F. Healy, J.J.P. Stewart, J. Am. Chem. Soc. 107 (1990) 3902.
[24] Hypercube, Inc., HyperChem 6.03 Package, Gainesville, FL, USA, 1999.