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Convenient synthesis of 3-aminomethylenedihydrofuran-2-ones

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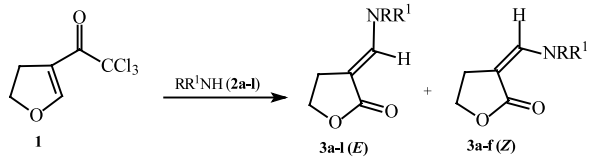
Abstract—A simple and convenient synthesis of a series of 3-aminomethylenedihydrofuran-2-ones from the reaction of 3-trichloroacetyl-4,5-dihydrofuran with amines, is presented.

3-Methylenedihydrofuran-2-ones are very well known compounds since a large number of publications are found in the literature dealing with synthetic aspects of these compounds.[1] However, 3-aminomethylenedihydrofuran-2-ones have been the subject of very few studies. On a search in the literature only four papers were found reporting the synthesis and/or applications of 3-aminomethylene-4,5-dihydrofuran-2-ones. The first synthesis of 3-aminomethylenedihydrofuran-2-ones was reported by Ozawa et al.[2] in 1959, that used these compounds to prepare some substituted 4-chloro-3-(2-chloroethyl)-2-methylquinolines. Lately, Korte et al.[3] reported the synthesis of a series of 3-aminomethylenedihydrofuran-2-ones from the reaction of 2-acylbutyrolactone with amines. More recently, Badawey and Kappe[4] reported the synthesis and biological evaluation of 3-aminomethylenedihydrofuran-2-ones as antineoplasmatic and cytotoxic compounds and used these molecules to prepare a series of 4-chloro-3-(2-chloroethyl)-2-methylquinolines. Another work reported a NMR study on some series of enamino ketones and esters including a couple of 3-aminomethylene-4,5-dihydrofuran-2-ones, however, the synthesis was not properly described.[5]

All synthesis of 3-aminomethylenedihydrofuran-2-ones described in the literature so far[2–4] relies on the condensation of 2-acylbutyrolactone and amines under reflux in toluene for 24 h. In this work, a new and more convenient method to synthesize 3-aminomethylenedihydrofuran-2-ones from the reaction of the readily available 3-trichloroacetyl-4,5-dihydrofuran[6] with amines is presented. The synthetic potential of 3-trichloroacetil-4,5-dihydrofuran for the synthesis of isoxazoles,[6] pyrazoles,[7] pyrimidines,[8–10] and analogues of cyclophosphamide,[11] has been reported.

The reaction of **1** with amines **2a–l** was carried out in an appropriate solvent (e.g. ethanol) in a molar ratio of 1:1, at room temperature (for **2a**,**c**,**h–l**) or at reflux (for **2b**,**d**,**e–g**) under stirring for 1 h (see Scheme 1 and Table 1). Other solvents such as dichloromethane, chloroform, or hexane were also tested but these solvents not always gave positive reaction or better yields, specially when amines in aqueous solution were used. Dichloromethane furnished better results when secondary amines were used. Reaction of **1** with amines **2d–g** carried out in dichloromethane or chloroform under reflux for 4 h showed a mixture of the desired 3-aminomethylenedihydrofuran-2-ones (**3**) and non identified impurities and reducing the reflux time unreacted starting materials were observed. From these results we concluded that for the reaction of **1** with primary amines ethanol is the most satisfactory solvent and with the secondary amines, dichloromethane. No reaction has been observed from **1** with aniline and benzylamine.



Scheme 1.

Keywords: 3-aminomethylenedihydrofuran-2-ones; 3-trichloroacetyl-4,5-dihydrofuran; amines.

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Table 1. Reaction conditions of **1** with amines **2a–l**

	Amine		Conditions	Yield (%)	Product composition (%) **3**-(*E*)/**3**-(*Z*)
	R	R^1			
2a	H	H	EtOH, rt, 1 h[a]	71	100[f]
2a	H	H	CH_2Cl_2, rt, 1 h[a]	[d]	
2b	CH_3	H	EtOH, reflux, 1 h[b]	75	90/10
2b	CH_3	H	CH_2Cl_2, rt, 1 h[b]	60	60/40
2b	CH_3	H	Hexane, reflux, 1 h[b]	72	100[f]
2c	CH_2CH_3	H	EtOH, rt, 1 h[c]	81	77/23
2c	CH_2CH_3	H	CH_2Cl_2, rt, 1 h[c]	65	60/40
2d	$(CH_2)_2CH_3$	H	EtOH, reflux, 1 h	89	77/23
2d	$(CH_2)_2CH_3$	H	CH_2Cl_2, rt, 1 h	[d]	
2d	$(CH_2)_2CH_3$	H	CH_2Cl_2, reflux, 4 h	[e]	
2d	$(CH_2)_2CH_3$	H	$CHCl_3$, reflux, 4 h	[e]	
2e	$CH(CH_3)_2$	H	EtOH, reflux, 1 h	75	77/23
2e	$CH(CH_3)_2$	H	CH_2Cl_2, rt, 1 h	[d]	
2e	$CH(CH_3)_2$	H	CH_2Cl_2, reflux, 4 h	[e]	
2e	$CH(CH_3)_2$	H	$CHCl_3$, reflux, 4 h	[e]	
2e	$CH(CH_3)_2$	H	Hexane, rt, 1 h	91	77/23
2f	$CH_2CH{=}CH_2$	H	EtOH, reflux, 1 h	78	77/23
2f	$CH_2CH{=}CH_2$	H	CH_2Cl_2, rt, 1 h	[d]	
2f	$CH_2CH{=}CH_2$	H	CH_2Cl_2, reflux, 4 h	[e]	
2f	$CH_2CH{=}CH_2$	H	$CHCl_3$, reflux, 4 h	[e]	
2g	CH_2CH_2OH	H	EtOH, reflux, 1 h	83	100[f,g]
2g	CH_2CH_2OH	H	CH_2Cl_2, rt, 1 h	[d]	
2g	CH_2CH_2OH	H	CH_2Cl_2, reflux, 4 h	[e]	
2g	CH_2CH_2OH	H	$CHCl_3$, reflux, 4 h	[e]	
2h	CH_3	CH_3	MeOH, rt, 1 h[a]	85	100[f]
2i	CH_2CH_3	CH_2CH_3	CH_2Cl_2, rt, 1 h	88	100[f]
2j	$-(CH_2)_4-$		CH_2Cl_2, rt, 1 h	92	100[f]
2k	$-(CH_2)_5-$		CH_2Cl_2, rt, 1 h	91	100[f]
2l	$-(CH_2)_2O(CH_2)_2-$		CH_2Cl_2, rt, 1 h	89	100[f]

[a] Amine in aqueous solution (~30%).
[b] Amine in aqueous solution (~40%).
[c] Amine in aqueous solution (~70%).
[d] No reaction was observed.
[e] Isolated **3** plus non-identified impurities.
[f] Only the isomer **3**-(*E*) was observed.
[g] NMR spectra registered in DMSO-d_6. NMR spectra of all other compounds were registered in $CDCl_3$.

The solvent used in the reactions seems to influence the proportion of **3**-(*E*)- and **3**-(*Z*)-isomers when primary amines were used (see Table 1). The reaction of **1** with primary amines carried out in ethanol furnished the **3**-(*E*)-isomer in much larger proportion than the **3**-(*Z*)-isomer while in dichloromethane an increase of the proportion of the **3**-(*Z*)-isomer was observed, although, the **3**-(*E*)-isomer is still the major component. Surprisingly, the reactions carried out in hexane furnished basically the same isomer ratio than in ethanol. However, it is well known that the population of the (*E*)- and (*Z*)-isomers of β-enamino ketones is largely dependent of the solvent in which the NMR spectrum was registered.[12–14] From the reaction of **1** with secondary amines **2h–l**, only the (*E*)-isomer was observed independent of the solvent used in the reactions.

The products of the reaction of **1** with amines in aqueous solution (**3a–c**) were isolated by extraction with dichloromethane and the products of the reactions of **1** with the other amines (**3d–l**) were isolated simply by evaporation of the reaction solvent. The products **3a–l** isolated as described, presented high purity when analyzed by ^{1}H NMR and GC–MS, showing no side products or starting material. Compounds were further purified by column chromatography on silica gel (230–400 mesh) using dichloromethane as the mobile phase. Compounds **3a–l** were analyzed by ^{1}H and ^{13}C NMR, IR, and GC–MS.[15] The composition of **3**-(*E*)- and **3**-(*Z*)-isomers presented in Table 1 was determined by ^{1}H NMR integrals.

The assignments of the (*E*)- and (*Z*)-isomers of compounds **3a–g** were based mainly on the ^{1}H NMR chemical shifts of the N–H, vinyl hydrogen, and comparison with literature data.[5] It was observed that the vinyl hydrogen of the **3**-(*E*)-isomer is about 0.5 ppm more deshielded than the same hydrogen of the **3**-(*Z*)-isomer, probably due to the diamagnetic anisotropy deshielding of the carbonyl. On the other hand, the N–H of the **3**-(*Z*)-isomer is about 2 ppm more deshielded than the **3**-(*E*)-isomer, probably due to the intramolecular hydrogen bonding with the carbonyl. Figure 1 shows a typical ^{1}H and ^{13}C NMR chemical

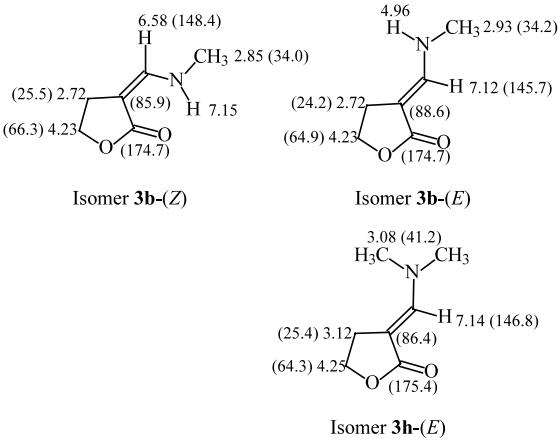
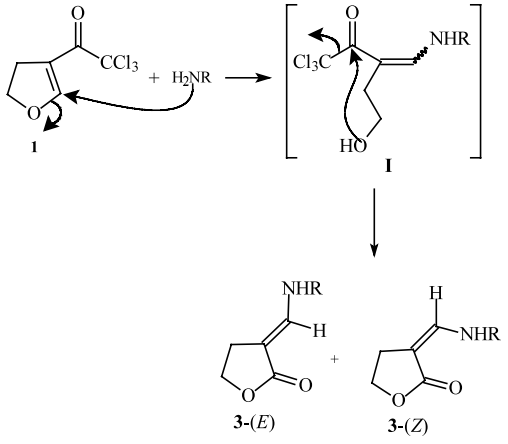


Figure 1. Typical ^{1}H and ^{13}C NMR chemical shifts of representative isomers of 3-aminomethylenedihydrofuran-2-ones.

shifts of representative isomers of 3-aminomethylenedihydrofuran-2-ones. The vinyl hydrogen of compounds **3h–l** (derived from the reaction of **1** with secondary amines) are in the same chemical shift range of the (*E*)-isomers of **3a–g**, so, compounds **3h–l** were assigned as (*E*)-isomers. The ^{13}C chemical shifts of **3b** are also in close agreement with those reported in the literature.[5]

The proposed mechanism of formation of **3** probably starts with a Michael addition of the *N*-nucleophile to the α,β-unsaturated ketone **1** and the subsequent ring opening (structure **I**, Scheme 2). The hydroxyl group undergoes intramolecular attack to the carbonyl displacing the trichloromethyl group leading to the 3-aminomethylenedihydrofuran-2-ones **3** as shown in Scheme 2.

In conclusion, we have developed a simple and effective methodology for the conversion of 3-trichloroacetil-4,5-dihydrofuran to 3-aminomethylenedihydrofuran-2-ones in a single reaction step, in mild conditions, and in high yields.



Scheme 2.

Acknowledgements

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15. The following are ^{1}H and ^{13}C NMR, IR, and GC–MS spectral data of representative compounds: (*E*)-**3a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.67 (td, $J=7.6$, 1.8 Hz, 2H, H-4), 4.18 (t, $J=7.6$ Hz, 2H, H-5), 4.90–5.0 (bs, 2H, NH_2), 7.12 (tt, $J=13.4$, 1.8 Hz, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.6 (C-4), 65.1 (C-5), 92.6 (C-3), 141.3 (C-6), 174.6 (C-2). MF (MW): $C_5H_7NO_2$ (113.11). GC–MS (EI, 70 eV) m/z (%): 113 (M^+, 55), 83 (28), 69 (16), 55 (100). (*Z*)-**3a**: ^{1}H NMR ($CDCl_3$, 200

MHz) δ 2.75 (td, $J=7.6$, 1.8 Hz, 2H, H-4), 4.15 (t, $J=7.6$ Hz, 2H, H-5), 7.30–7.50 (bs, 2H, NH_2), 6.75 (tt, $J=13.4$, 1.8 Hz, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.5 (C-4), 66.4 (C-5), 89.3 (C-3), 143.8 (C-6), 174.6 (C-2).

(*E*)-**3b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.62–2.79 (m, 2H, H-4), 2.94 (d, $J=4.8$ Hz, 3H, NCH_3), 4.24 (t, $J=7.6$ Hz, 2H, H-5), 4.8–4.9 (bs, 1H, N-H), 7.12 (dt, $J=13.4$, 1.8 Hz, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.2 (C-4), 34.2 (NCH_3), 64.9 (C-5), 88.6 (C-3), 145.7 (C-6), 174.7 (C-2). MF (MW): $C_6H_9NO_2$ (127.14). GC–MS (EI, 70 eV) m/z (%):127 (M^+, 74), 98 (22), 82 (25), 68 (100), 54 (11). IR (neat), ν (cm^{-1}): 3418, 3053, 1716, 1647, 1264.

(*Z*)-**3b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.62–2.79 (m, 2H, H-4), 2.89 (d, $J=4.8$ Hz, 3H, NCH_3), 4.23 (t, $J=7.6$ Hz, 2H, H-5), 6.60 (dt, $J=13.4$, 1.8 Hz, 1H, H-6), 7.05–7.10 (bs, 1H, N-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.5 (C-4), 34.0 (NCH_3), 66.3 (C-5), 85.9 (C-3), 148.4 (C-6), 174.7 (C-2).

(*E*)-**3f**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.75 (td, $J=7.6$, 1.8 Hz, 2H, H-4), 3.70–3.90 (m, 2H, NCH_2), 4.30 (t, $J=7.6$ Hz, 2H, H-5), 4.90–5.00 (bs, 1H, N-H), 5.10–5.30 (m, 2H, NCC=CH_2), 5.78–5.96 (m, 1H, NCCH=), 7.22 (dt, $J=13.4$, 1.8 Hz, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.2 (C-4), 50.3 (NCH_2), 64.9 (C-5), 89.9 (C-3), 116.8 (NCC=CH_2), 134.7 (NCCH=), 144.2 (C-6), 174.4 (C-2). MF (MW): $C_8H_{11}NO_2$ (153.18). GC–MS (EI, 70 eV) m/z (%): 153 (M^+, 100), 124 (29), 108 (80), 94 (83), 80 (36), 68 (32). IR (neat), ν (cm^{-1}): 3415, 3054, 1722, 1650, 1264. (*Z*)-**3f**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.83 (td, $J=7.6$, 1.8 Hz, 2H, H-4), 3.70–3.90 (m, 2H, NCH_2), 4.30 (t, $J=7.6$ Hz, 2H, H-5), 7.30–7.45 (bs, 1H, N-H), 5.10–5.30 (m, 2H, NCC=CH_2), 5.78–5.96 (m, 1H, NCCH=), 6.67 (dt, $J=13.4$, 1.8 Hz, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.6 (C-4), 50.1 (NCH_2), 66.4 (C-5), 87.1 (C-3), 116.5 (NCC=CH_2), 134.9 (NCCH=), 146.8 (C-6), 174.5 (C-2).

(*E*)-**3g**: ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.81 (td, $J=7.6$, 1.8 Hz, 2H, H-4), 3.37 (dt, $J=7.6$, 5.2 Hz, 2H, NCH_2), 3.70 (t, $J=5.2$ Hz, 2H, $NCCH_2OH$), 4.34 (t, $J=7.6$ Hz, 2H, H-5), 5.86–5.92 (m, 1H, N-H), 7.28 (dt, $J=13.4$, 1.8 Hz, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.6 (C-4), 49.7 (NCH_2), 60.7 ($NCCH_2OH$), 63.9 (C-5), 87.3 (C-3), 144.6 (C-6), 173.6 (C-2). MF (MW): $C_7H_{11}NO_3$ (157.16). GC–MS (EI, 70 eV) m/z (%): 157 (M^+, 35), 139 (12), 126 (100), 108 (25), 98 (25), 80 (20), 68 (28), 53 (25).

(*E*)-**3h**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.05 (s, 6H, NCH_3), 3.12 (t, $J=7.8$ Hz, 2H, H-4), 4.25 (t, $J=7.8$ Hz, 2H, H-5), 7.14 (s, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.4 (C-4), 41.2 (NCH_3), 64.3 (C-5), 86.4 (C-3), 146.8 (C-6), 175.4 (C-2). MF (MW): $C_7H_{11}NO_2$ (141.16). GC–MS (EI, 70 eV) m/z (%): 141 (M^+, 78), 126 (17), 112 (22), 96 (65), 82 (100), 68 (16). IR (neat), ν (cm^{-1}): 3053, 1720, 1626, 1264.

(*E*)-**3i**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, $J=7.6$ Hz, 6H, $NCCH_3$), 3.04 (t, $J=7.6$ Hz, 2H, H-4), 3.30 (q, $J=7.6$ Hz, 4H, NCH_2), 4.26 (t, $J=7.6$ Hz, 2H, H-5), 7.18 (s, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5 ($NCCH_3$), 25.6 (C-4), 45.9 (NCH_2), 64.3 (C-5), 85.4 (C-3), 145.2 (C-6), 175.7 (C-7). MF (MW): $C_9H_{15}NO_2$ (169.22). GC–MS (EI, 70 eV) m/z (%): 169 (M^+, 49), 154 (38), 140 (100), 122 (18), 110 (21), 96 (53), 82 (21), 64 (27), 56 (37). IR (neat), ν (cm^{-1}): 3054, 1716, 1617, 1265.

(*E*)-**3j**: mp 110–112°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.92 (t, $J=6.4$ Hz, 4H, $NCCH_2$), 3.15 (t, $J=7.6$ Hz, 2H, H-4), 3.56 (t, $J=6.4$ Hz, 4H, NCH_2), 4.24 (t, $J=7.6$ Hz, 2H, H-5), 7.37 (s, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.2 (C-4), 25.6 ($NCCH_2$), 49.9 (NCH_2), 64.6 (C-5), 87.4 (C-3), 143.2 (C-6), 175.3 (C-2). MF (MW): $C_9H_{13}NO_2$ (167.20). GC–MS (EI, 70 eV) m/z (%): 167 (M^+, 86), 139 (23), 122 (100), 108 (25), 94 (29), 81 (39), 54 (21). IR (KBr pellets), ν (cm^{-1}): 3055, 1707, 1630, 1270.

(*E*)-**3l**: mp 84–86°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.03 (t, $J=7.6$ Hz, 2H, H-4), 3.43 (t, $J=6.4$ Hz, 4H, NCH_2), 3.70 (t, $J=7.6$ Hz, 4H, $NCCH_2O$), 4.28 (t, $J=7.6$ Hz, 2H, H-5), 7.10 (s, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.8 (C-4), 49.5 (NCH_2), 64.4 (C-5), 66.3 ($NCCH_2O$), 87.8 (C-3), 145.0 (C-6), 175.3 (C-7). MF (MW): $C_9H_{13}NO_3$ (183.20). GC–MS (EI, 70 eV) m/z (%): 183 (M^+, 100), 165 (21), 152 (34), 140 (31), 124 (39), 112 (32), 98 (62), 80 (44), 67 (38). IR (KBr pellets), ν (cm^{-1}): 3054, 1713, 1624, 1269.