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Base Promoted Reactions of 4-Pentynones.

Antonio Arcadi*[a], Fabio Marinelli[a], Elena Pini[b], Elisabetta Rossi*[b].

[a] Dipartimento di Chimica Ingegneria Chimica e Materiali , Università di L'Aquila, Via Vetoio, Coppito Due, I-67100 L'Aquila, Italy

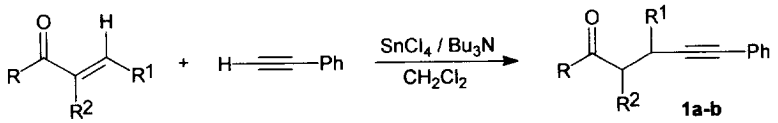
[b] Istituto di Chimica Organica della Facoltà di Farmacia, Università di Milano, Via Venezian 21, I-20139 Milano, Italy

Abstract: Different substituted furans are syntetised by cyclization of 4-pentynones using potassium *tert*-butoxide in DMF. A different reaction pattern is observed when the same compounds were treated with sodium methoxide in MeOH. A new approach to 2-propargyl-carbonyl compounds is also proposed. Copyright © 1996 Elsevier Science Ltd

The synthesis of many different substituted furan derivatives has been achieved by the intramolecular cyclization of acyclic precursors. Several of these methods involve the intramolecular attack of a nucleophilic oxygen over an alkyne functionality[1,2] and among them, some examples of acid[3] or transition metal[4] mediated cyclization of enolizable ynones have appeared recently in the literature. Moreover, the synthesis of furans by base-catalysed cyclization of activated 4-pentynones has been recently reported.[5]

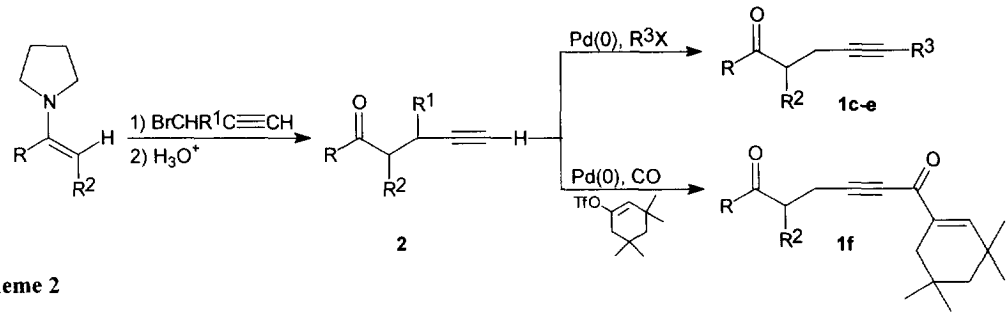
In connection with our ongoing interest in developing new synthetic strategies for the construction of five-membered heterocyclic rings involving alkyne derivatives[6], we thought that the regioselective intramolecular *exo-dig* cyclization of 4-pentynones could represent a general procedure for the synthesis of functionalised furans. We wish to report the preliminary results of this investigation.

Starting compounds **1a-b** were prepared by alkynylation of the corresponding α,β-unsaturated ketones[7] (Scheme 1, Table 1).



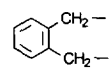
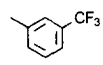
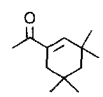
Scheme 1

Although the preparation of **1a** and **1b** was possible by this method, the synthesis of **1c-f** failed. Instead, an alternative strategy was employed involving terminal α-propargylketones **2**, obtained by Stork enamine reaction with propargyl bromide[8], as starting building blocks. In particular, compounds **1c-f** were prepared from **2** through palladium-catalysed coupling reactions[9] (**1c-e**) or a carbonylative palladium-catalysed reaction[10] (**1f**), (Scheme 2, Table 1).



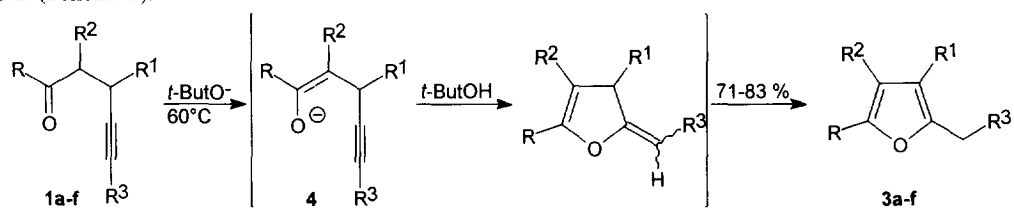
Scheme 2

Table 1. 4-Pentynones **1a-f**.

1	Yield	R	R^2	R^1	R^3	1	Yield	R	R^2	R^1	R^3
a	57[a]	Ph	H	Ph	Ph	d	43[b]			H	
b	65[a]	CH=CHPh	H	Ph	Ph	e	93[b]	CH_2Ph	Ph	H	
c	55[b]	$-(CH_2)_4-$	H			f	50[b]	CH_2Ph	Ph	H	

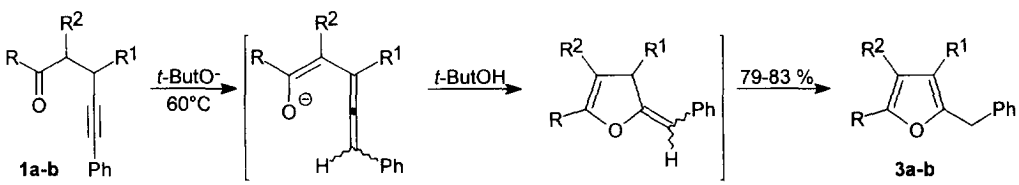
[a] Reported yield[7]: **1a** (57%), **1b** (74%). [b] From α-propargylketone **2**.

The expected furan derivatives[11] **3a-f** were obtained in good yields by reacting **1a-f** with t-BuOK in dry DMF (Scheme 3).



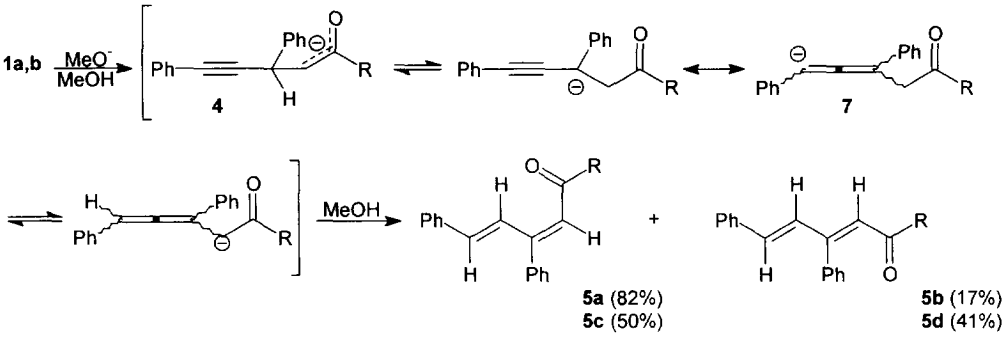
Scheme 3

The reaction mechanism probably involves a 5-*exo-dig* cyclization of the enolate **4** over the carbon-carbon triple bond followed by tautomerization to give furans **3a-f**. However, for compounds **1a-b**, bearing a phenyl substituent at the triple bond, a second mechanism involving a highly reactive allene intermediate cannot be excluded, Scheme 4.[2]



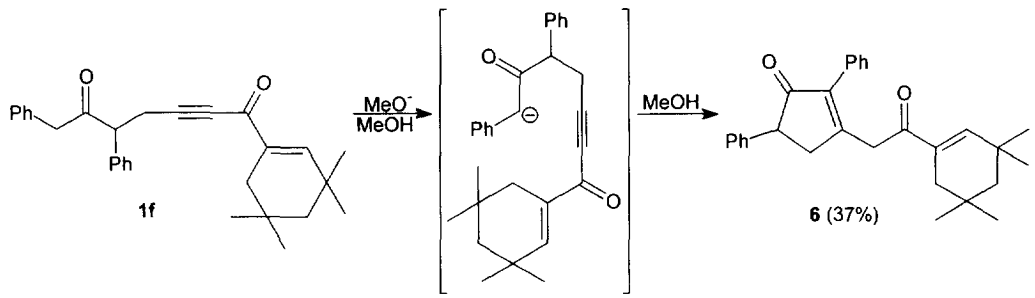
Scheme 4

When the same compounds **1a-f** were reacted with MeONa (1.2 mol) in MeOH at 60 °C a different reaction pattern was observed. Compounds **1a** and **1b** gave respectively the (E,E) and (Z,E)-1,3,5-triphenyl-penta-2,4-dien-1-ones **5a** and **5b** and the (E,E,E) and (E,Z,E)-1,5,7-triphenyl-epta-1,4,6-trien-3-ones **5c** and **5d** (Scheme 4). The structures of **5a-d** were assigned on the basis of ^{1}H-NMR analysis[12]. Moreover, whereas compounds **1c-e** were recovered unreacted even after prolonged reaction time, compound **1f** gave the 2-cyclopentenone **6**[13]. These results can be rationalised taking into account the relative reactivity of the enolate **4** in different medium. A polar aprotic solvent such DMF, which is very effective in solvating cations, increases the reactivity of the more electronegative atom of the enolate **4**. On the contrary, when the reactions are performed in methanol, where the enolate **4** is hydrogen-bonded by solvent, the anion **4**, generated from compounds **1a** and **1b**, probably isomerizes to the corresponding anionic allene **7**; subsequent prototropic shift and allene-diene isomerization affords the final products **5a-d**, (Scheme 5).



Scheme 5

A different behaviour was shown by the carbanion of **1f** which carbocyclizes through a conjugated addition over the activated triple bond giving rise to the 2-cyclopentenone **6** (Scheme 6).



Scheme 6

The influence of the reaction medium is supported by the results obtained when compounds **1a** and **1f** were treated with sodium methoxide (1.2 mol) in a non-protic solvent such DMF. Under these conditions furans **3a** and **3f** were obtained as the sole reaction products.

In conclusion, in this work we reported an efficent synthesis of simple and polycondensate furans starting from different substituted pentynones and described for these compounds unusual base-catalysed reactions. A new approach to the synthesis of 4-pentynones and 2-pentyn-1,6-diones is also proposed. Further work is in progress to define the scope and limitations of these reactions.

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11. Synthesis of **3a**, general procedure: to a well stirred suspension of potassium *tert*-butoxide (1.2 mmol, 135 mg) in dry DMF (1 ml) a solution of 1,3,5-triphenyl-4-pentyn-1-one **1a** (1 mmol, 310 mg) in dry DMF (2 ml), was added. The mixture was stirred at 60°C for 3h and then poured in HCl 0.1 N (50 ml)/EtOAc (50 ml). The organic layer was separated and the aqueous phase extracted twice with EtOAc. The combined organic phases, dried over Na_2SO_4, were evaporated to dryness and the crude **3a** purified by flash chromatography over silica gel eluting with hexane/EtOAc (98:2). Yield: 83%. ^{1}H-NMR (200 MHz, $CDCl_3$, δ from TMS,): 4.17 (2H, s, CH_2); 6.78 (1H, s, H-3); 7.10-7.40 (13H, m, arom.); 7.63-7-70 (2H, m, arom.). EI-MS (m/z): 310 (M^+, 66), 233 (15), 105 (100), 77 (86).
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13. ^{1}H-NMR data of compound **6** (200 MHz, $CDCl_3$, δ from TMS, J = Hz): 0.94 (6H, bs, CH_3); 1.02 (6H, bs, CH_3); 1.35 (2H, s, CH_2); 2.02 (2H, s, CH_2); 2.84 (1H, dd, J=2, 19, CH_2); 3.16 (1H, dd, J=7, 19, CH_2); 3.75 (1H, dd, J=2, 7, CH); 3.98 (2H, AB system, J=16, CH_2CO); 6.45 (1H, s, vinyl H); 7.18-7.43 (10H, m, arom.). ^{13}C-NMR data of compound **6** (50.3 MHz, $CDCl_3$, δ from TMS): 29.5, 29.6, 30.6 and 30.7 (CH_3); 30.1 and 33.8 (quat. aliph. C); 36.2, 39.8 and 40.7 (CH_2); 49.0 (CH_2CO); 51.5 (CH); 126.8, 127.6, 128.1, 128.4, 128.7, 129.1, 131.3, 135.1, 139.7, 141.2, 150.0 and 167.7 (Csp_2); 197.0 and 206.0 (CO).

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