

TANDEM NUCLEOPHILIC REACTION LEADING TO HYDROFURANS: APPLICATION TO ONE-POT SYNTHESIS OF ANTITUMOR NAPHTHOFURAN NATURAL PRODUCT

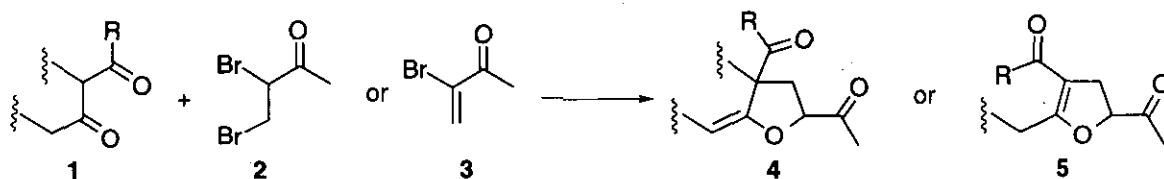
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Abstract –The reaction of enolates of 1,3-dicarbonyl compounds (**1**) with 3,4-dibromo-2-butanone (**2**) afforded hydrofuran derivatives (**4**) or (**5**) in the presence of DBU in THF and the reaction was applied to the one-pot synthesis of antitumor naphthofuran natural products (**29**).

The furan and hydrofuran moieties are important functional groups and several bio-active natural products invariably possess them as a part of their structural feature.¹ Although, a number of methods are available to effect their synthesis, the search for newer methods is continuously being pursued to develop efficient and short synthetic procedures.²

In continuation of our interest to effect hydrofuran synthesis³ through tandem nucleophilic reactions,⁴ we delineate herein a novel synthetic protocol towards 2-acetylhydrofuran derivatives (**4**) or (**5**) involving the reaction of 1,3-dicarbonyl compounds (**1**) with 3,4-dibromo-2-butanone (**2**) (Scheme 1). The acetylhydrofuran derivatives so formed would function as a versatile intermediate for further transformations.

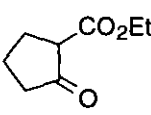
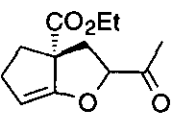
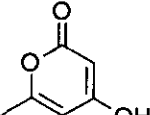
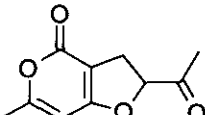
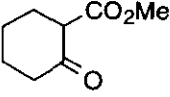
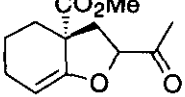
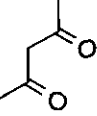
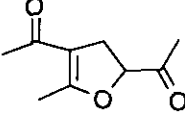
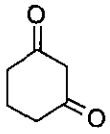
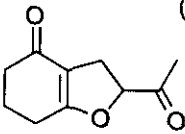
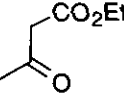
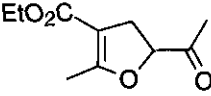
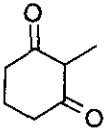
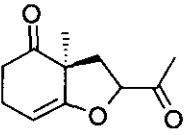
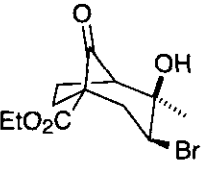


Scheme 1

Our initial plan of utilizing **3** as the halocarbonyl Michael acceptor was soon abandoned because of its difficulty in its preparation. Consequently, we employed its stable precursor 3,4-dibromo-2-butanone (**2**)⁵ to generate *in situ* the required reactive substrate (**3**) in the reaction pot itself. As a matter of fact, the formation of **3** from **2** can be easily demonstrated by treating the CDCl_3 solution of **2** in an NMR tube with one equivalent of DBU followed by scanning the spectrum. The dibromide (**2**) was freshly prepared by bromination of 3-buten-2-one in pentane just prior to use.

The reaction of various 1,3-dicarbonyl compounds (**1**) with 3,4-dibromo-2-butanone (**2**) was carried out in THF using more than 2 eq. of DBU as the base (Table 1).³

Table 1. Reactions of 1,3-dicarbonyl compounds with 3,4-dibromo-2-butanone (**2**).

Entry	Starting Material	Product (%)	Entry	Starting Material	Product (%)
1		 72^{a,b} (70:30)^c 55^d	5		 34
2		 59^b (65:35)	6		 87
3		 40	7		 57
4		 35^b (82:18)^c			20

^a Reaction was carried out in THF with 2.3 eq. of DBU at $-25^{\circ}\text{C} \rightarrow \text{rt}$ for 43 h.

^b A mixture of diastereomer was obtained.

^c Ratio was determined by NMR spectrum.

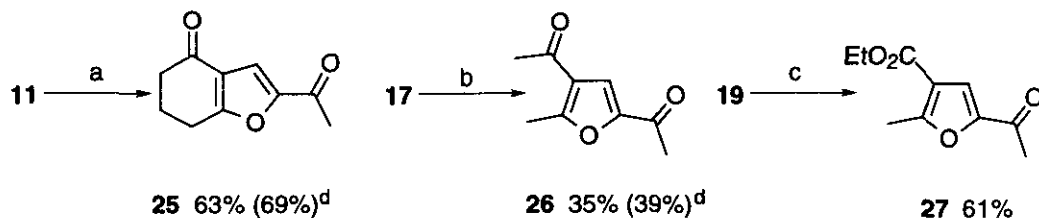
^d Single diastereomer was obtained along with bicyclic compound (**20**) (38%) when reaction was quenched at -25°C for 3.8 h.

Both cyclic and acyclic dicarbonyl compounds gave satisfactory yield of the respective acetylhydrofuran derivatives in one-pot operation. In case of 2-carboethoxycyclopentanone (**6**), in addition to the hydrofuran derivative (**7**), a bicyclo[3.2.1]octane derivative (**20**) was also isolated as a by-product of the reaction, the formation of which can be rationalized as Michael addition followed by intramolecular aldol reaction. In this case, prolonged reaction time enabled to shift the equilibrium of the reaction from aldol adduct (**20**) back to intermediary Michael addition product, which cyclized irreversibly to the desired acetylhydrofuran derivative (**7**). This result indicates that the present reaction

proceeds *via* tandem Michael-*O*-alkylation reaction. Relative stereochemistry of one diastereomer of hydrofuran (**7**) could not be determined after extensive NOE experiment. Diastereomers of other hydrofurans (**9**) and (**13**) were inseparable by medium pressure liquid chromatography.

Tough oxidation of the hydrofurans (**11**), (**17**) and (**19**) to their respective furan derivatives (**25**)–(**27**) resulted in recovery of hydrofurans, the transformation was achieved through the procedure of Williams⁶ employing BrCCl₃ and DBU in THF (Figure 1).

Figure 1. Preparation of furan.

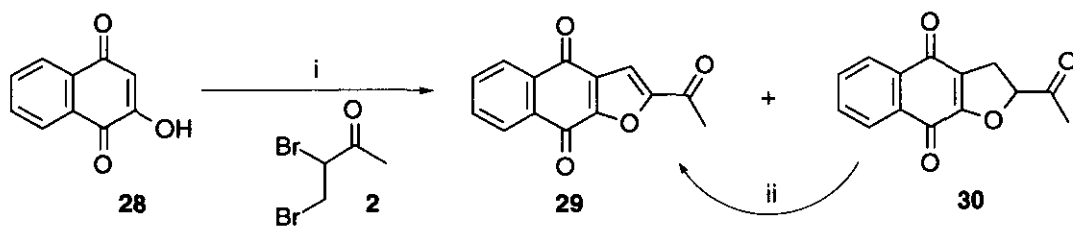


The reaction conditions are as follows. ^a 0 °C~rt, 21 h; ^b 0~50 °C, 43 h; ^c 0 °C~rt, 19 h

^d Yield in parenthesis is based on starting material consumed.

Synthesis of antitumor naphthofuran natural product.

In order to demonstrate the versatility of our new procedure to effect synthesis of natural products containing furan moiety, we report herein a one-pot synthesis of a naphthofuran natural product (**29**) which was isolated from stem bark of *Tabebuia cassinoids* (Lam.) DC. (Bignoniaceae) with pronounced anti-cancer activity.⁷ Although, there were reports on the synthesis of the natural product (**29**),⁷⁻⁹ it was worthwhile to test the synthetic utility of our own procedure by extending the protocol towards (**29**). Accordingly, commercially available 2-hydroxy-1,4-naphthoquinone (**28**) with 3,4-dibromo-2-butanone (**2**) underwent cyclization with DBU to afford not only naphthohydrofuran derivative (**30**) but also the desired natural product (**29**) in 28% yield (Scheme 2). Moreover, the naphthohydrofuran derivative (**30**) was transformed into the natural product (**29**) in 43% yield by the procedure of Williams.⁶ The mechanism which leads directly to **29** is not clear at present. DDQ oxidation of the naphthohydrofuran derivative (**30**) resulted in decomposition of the substrate, thereby suggesting that **29** is not formed *via* oxidation by quinone (**28**). The spectral data of the compound (**29**) showed good agreement with those reported for the natural product (NMR, IR, Ms, and UV).⁷



Scheme 2

Reagents and conditions: i, DBU, THF, rt, 10 h, **29** 28%, **30** 37%, ii, BrCCl₃, DBU, CH₂Cl₂, -20~rt., 5 h, 43%.

In conclusion, we have demonstrated that the tandem nucleophilic reactions involving both carbon and oxygen termini of enolates derived from 1,3-dicarbonyl compounds (**1**) with 3-bromo-3-buten-2-one (**3**) generated *in situ* provided an efficient route to substituted acetylhydrofuran derivatives in moderate yields. Further, our protocol has been applied to effect one-pot synthesis of a naphthofuran based bioactive natural product thereby demonstrating the versatility of the newly developed procedure.

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