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# Efficient Synthesis of Tetrasubstituted Furans from Nitroallylic Acetates and 1,3-Dicarbonyl/α-Activating Ketones by Feist–Bénary Addition–Elimination

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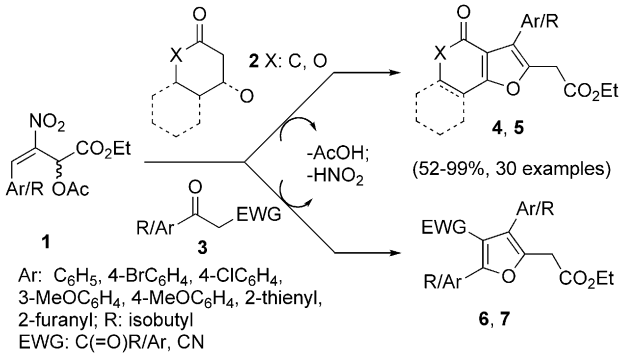
Furans represent an important subclass of five-membered aromatic heterocycle that has been used for the synthesis of many pharmaceutical molecules[1] and industrial materials.[2] The functionalization of furans often allows for further structural elaboration and adornment. As a consequence, many valuable synthetic protocols have been devised for the construction of polysubstituted furans, and these are based either on introducing substituents onto the existing furan ring or furan ring construction from acyclic precursors.[3] Derivatization of furans often requires the application of a metal–halogen exchange reaction or a transition-metal-catalyzed cross-coupling,[4a,b] with the halide precursor emanating from an electrophilic substitution process.[4c] On the other hand, some excellent methods have been developed for the build-up of functionalized furans from acyclic precursors, some of which utilize alkynyl epoxides,[5a] α-alkenyl-β-diketones,[5b] cyclopropenyl ketones,[5c] γ-acyloxy butynoates,[5d] alkynyl ketones,[5e] β-acyloxy acetylenic ketones,[5f] α-alkynyl enones,[5g–o] thioalkynone,[5p] alkynol/alkyne,[5q–s] alkynoate/1,3-dicarbonyls,[5t] propargylic alcohols/1,3-dicarbonyls,[5u] propargylic alcohols/ketones,[5v] allenyl ketones,[5w] propargylic esters,[5x] propargyl vinyl ethers,[5y] alkynyl cyclopropyl ketones,[5z–aa] alkenyl carbene/enones,[5ab] β-alkynyl enals,[5ac] acyloxy sulfones,[5ad] enynols,[5ae–af] and various other substrates.[5ag] The application of these methods often requires the preparation of specially tailored starting substrates utilizing transition-metal catalyzed reactions. The Paal–Knorr reaction has proven particularly useful for furan ring assembly.[6] The reaction of 1,3-dicarbonyl compounds with α-haloketones (the Feist–Bénary reaction) under metal-free conditions, is another longstanding historical protocol that has provided rapid access to many different types of substituted furans.[7]

The development of facile new methods for the efficient ring assembly of tetrasubstituted furans remains a highly desirable and challenging objective for many in the field. We present herein a unique and generally efficient synthetic strategy for accessing tetrasubstituted furans that exploits a Feist–Bénary type reaction between electron-deficient nitroallylic acetates **1** and 1,3-dicarbonyl/α-activating ketones. The corresponding multifunctional 3,5-alkyl/aryl-2-carboxylate-4-keto/cyano-containing tetrasubstituted furans were typically obtained in respectable to excellent yield (52–99%) via an interesting $S_N2'$ addition–elimination sequence that proceeds under very mild reaction conditions [Eq. (1)].




Initially we investigated the synthesis of ring-annulated furan **4a** from nitroallylic acetate **1a**[8] and cyclohexan-1,3-diketone **2a** as a model reaction. Treatment of **1a** and **2a** with $Et_3N$ in $CH_3CN$ for 48 h at room temperature gave ethyl-2-(4,5,6,7-tetrahydro-4-oxo-3-phenylbenzofuran-2-yl)acetate **4a** in 73% yield (Table 1, entry 1). Similar yields were observed when the reaction was carried out in the presence of DABCO or DBU (Table 1, entries 2–4), but with DIPEA over 72 h, a significant jump in yield was recorded. We next examined the influence of different inorganic bases on the reaction outcome. Yields dropped when $NaHCO_3$ was used as the base, while $Na_2CO_3$ led to the tetrasubstituted furan **4a** in 80% yield (Table 1, entries 5,6). The yield could be further improved to 94% when $K_2CO_3$ was employed as a base (Table 1, entry 7), and an almost quantitative yield was obtained when $Cs_2CO_3$ was used in $CH_3CN$ over 4 h (Table 1, entry 8). In an effort to further increase the reaction rate, various solvents were examined in this process. However, changes to the original solvent we had selected failed to improve the reactivity (Table 1, entries 9–11). The functionalized tetrasubstituted furan **4a** was fully characterized by IR and $H^1$ and $C^{13}$ NMR spectroscopic analysis and further confirmed by single-crystal X-ray analysis.[9]

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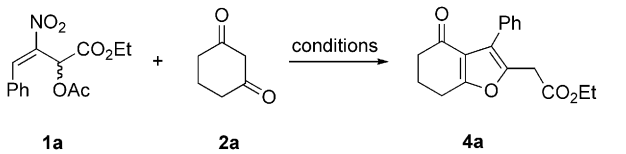
Table 1. Optimization of the reaction conditions.[a]




**1a** **2a** **4a**

| Entry | Base | Solvent | $t$ [h] | Yield [%][b] |
|---|---|---|---|---|
| 1 | $Et_3N$ | $CH_3CN$ | 48 | 73 |
| 2 | DABCO | $CH_3CN$ | 72 | 76 |
| 3 | DIPEA | $CH_3CN$ | 72 | 87 |
| 4 | DBU | $CH_3CN$ | 36 | 65 |
| 5 | $NaHCO_3$ | $CH_3CN$ | 48 | 52 |
| 6 | $Na_2CO_3$ | $CH_3CN$ | 48 | 80 |
| 7 | $K_2CO_3$ | $CH_3CN$ | 48 | 94 |
| **8** | **$Cs_2CO_3$** | **$CH_3CN$** | **4** | **99** |
| 9 | $Cs_2CO_3$ | toluene | 16 | 75 |
| 10 | $Cs_2CO_3$ | dioxane | 24 | 94 |
| 11 | $Cs_2CO_3$ | DMSO | 2 | 89 |

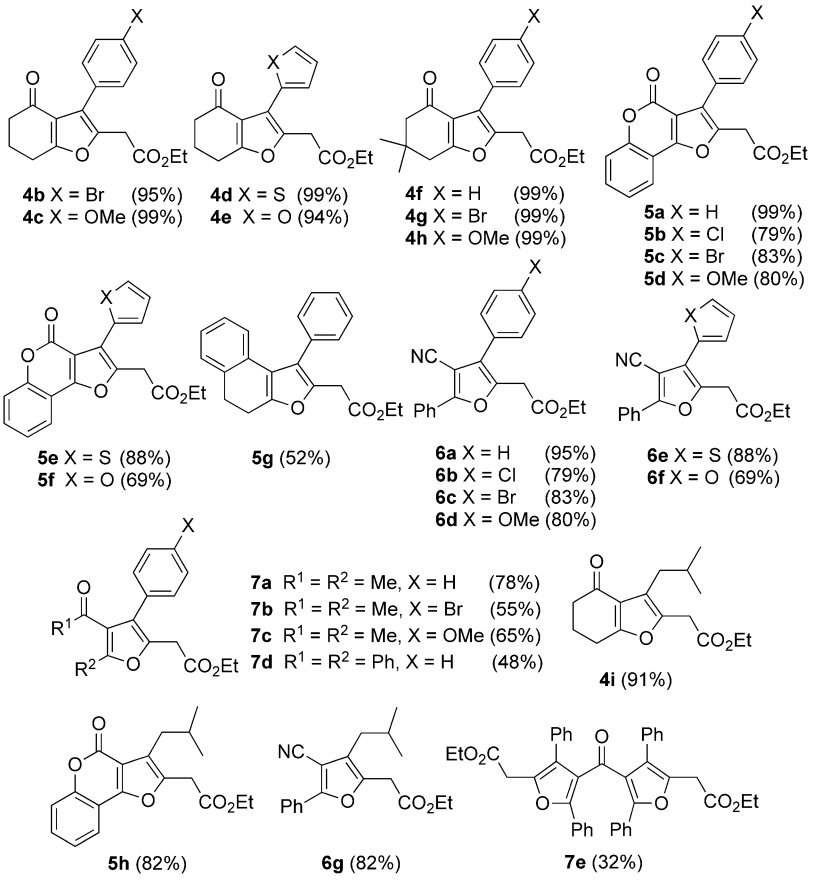
[a] All reactions were performed using nitroallylic acetate **1a** (31.4 mg, 0.11 mmol), cyclohexan-1,3-diketone **2a** (1.0 equiv), and base (1.0 equiv) in the indicated solvent at ambient temperature. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine. [b] Yield of isolated product.

With the optimum reaction conditions now secured, we next studied the feasibility and scope of our new reaction protocol. Various nitroallylic acetates **1** and 1,3-dicarbonyls (**2**)/α-activating ketones (**3**) were systematically investigated. For the cyclic 1,3-diketone substrates, various aryls and heteroaromatic substituents in the nitroallylic acetates were investigated and found to give satisfactory results (Scheme 1, **4b–e**). The use of 5,5-dimethylcyclohexane-1,3-dione as the Michael donor for the reaction also gave the desired products with excellent efficiency (**4f–h**).

Encouraged by these results, the reaction scope was further extended to chroman-2,4-dione. Treatment of **1a** with chroman-2,4-dione, under the optimum conditions, gave the corresponding 4H-furano[3,2-c]chromen-4-one **5a** in quantitative yield. This new furan ring construction method was also tolerant of various aryl and heteroaromatic substituents in the nitroallylic acetates (**5b–f**). The use of a less acidic β-tetralone as the nucleophilic component afforded the 4,5-dihydronaphtho[2,1-b]furan **5g** in 52% yield. 3-Oxo-3-phenylpropanenitrile likewise served as a good Michael donor for the desired addition–elimination process. Furans with 2-carboxylate-4-cyano-3,5-diaryl substituents could additionally be synthesized in high to excellent yield (Scheme 1, **6a–f**).

When pentane-2,4-dione was employed in this protocol, yields were typically lower. The desired polyfunctionalized 3-aryl-2-carboxylate-4-keto-5-methyl furans were isolated in yields that ranged from 55 to 78% (**7a–c**), and a further drop in yield was noted when 1,3-diphenylpropane-1,3-dione was employed in this process to obtain **7d**. The steric hindrance of the aryl substituents at the C3–5 positions might contribute significantly to the low yield observed in this transformation. Our Michael donors also reacted satisfactorily when there was an alkyl substituent in the nitroallylic acetate component (e.g. **4i**, **5h**, and **6g**). In yet another investigation of the scope of our method, we undertook the synthesis of some fully substituted bis(furan) compounds. Reaction of nitroallylic acetates with 1,3-dibenzoylacetone proceeded slowly to give the polyfunctionalized C2 symmetric bis(furan) species **7e** in 32% yield after 10 days.

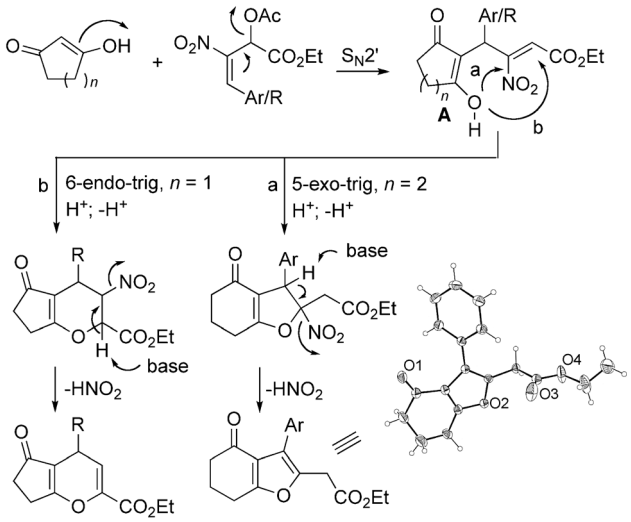
A definitive mechanistic explanation of the furan ring assembly process is unclear at the present moment, but one possible pathway is as follows: The nucleophilic enol first reacts with the Michael acceptor to give adduct **A** by an




Scheme 1. The structures of the tetrasubstituted furans.

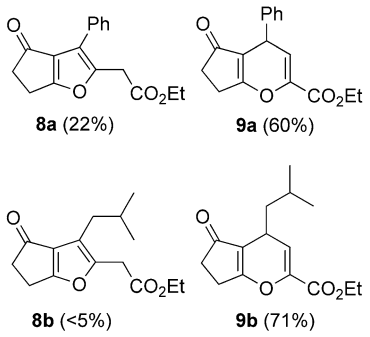
$S_N2'$ process (Scheme 2). This is followed by a second Michael addition from the enol oxygen atom to give the five-membered ring (5-*exo-trig* addition, route a). Deprotonation




Scheme 2. Mechanistic rationale for formation of substituted furan and pyran rings.

and elimination of $HNO_2$ then completes the process. The preferential formation of a five-membered ring over a six-membered ring (except cyclopentane-1,3-dione, see below) is consistent with Baldwin's rules.[10] The energetically favored aromatization of the furan core scaffold might also be contributing in a beneficial way.

The aforementioned addition–elimination process for the synthesis of furans is impressive. The inherent 1,3-C,O-nucleophilic nature in the donor component is essential for the reaction. In parallel, pyran ring formation in the second Michael reaction predominated when cyclopentane-1,3-dione was used (Scheme 2, by 6-*endo-trig* addition; route b). In this particular system, treatment of the nitroallylic acetate **1a** with 1,3-cyclopentanedione under the same reaction conditions provided the tetrasubstituted furan **8a** in only 22% yield, with the major product being the cyclopenta[b]pyran-2-carboxylate **9a** (60%; Scheme 3).[11] The structure of the cyclopenta[b]pyran was characterized by its $^1H$, $^{13}C$, and 2D




Scheme 3. The formation of cyclopenta[b]pyran-2-carboxylates **9a**,**b**.

NMR spectra. Interestingly, when isobutyl-substituted nitroallylic acetate was used, formation of the *endo* addition product **9b** predominated, and the compound could be isolated in 71% yield. The reversal of the preference for which ring forms (5- vs. 6-membered) is noteworthy. This reversal might arise from the special geometry of the resulting five-membered keto-enol conformation.

In summary, we have developed an efficient synthesis of tetrasubstituted furans via a Feist–Bénary type reaction. The Michael–Oxa–Michael–aromatization protocol of nitroallylic acetates with 1,3-dicarbonyls and α-activating ketones readily gives 3,5-alkyl/aryl-2-carboxylate-4-keto/cyano functionalized furans in good to excellent yield. Our new method now provides yet another powerful alternative for the synthesis of furans having diverse substitution patterns under mild reaction conditions. Other synthetic applications of nitroallylic acetates are currently under investigation in our laboratory.

## Experimental Section

*General procedure for synthesis tetrasubstituted furans*

(*E*)-Ethyl-2-acetoxy-3-nitro-4-phenylbut-3-enoate **1a** (0.11 mmol, 31.4 mg) was added to a stirred solution of 1,3-cyclohexanedione **2a** (0.11 mmol, 12.4 mg) and cesium carbonate (0.11 mmol, 36.0 mg) in $CH_3CN$ at room temperature. The mixture was stirred until the starting material disappeared as determined by TLC. The crude residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate = 3:1) to give the corresponding ethyl-2-(7-oxo-2-phenyl-4,5,6,7-tetrahydrobenzofuran-3-yl)acetate **4a.** $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.29–7.42 (m, 5H), 4.19 (q, 2H, $J$ = 7.2 Hz), 3.63 (s, 2H), 2.91 (t, 2H, $J$ = 6.6 Hz), 2.49 (t, 2H, $J$ = 6.6 Hz), 2.18 (quin, 2H, $J$ = 6.6 Hz), 1.27 ppm (t, 3H, $J$ = 7.2 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 193.6, 169.2, 166.5, 144.6, 130.9, 129.6 (x2), 127.9 (x2), 127.5, 122.2, 119.7, 61.3, 38.5, 32.4, 23.6, 22.3, 14.1 ppm; HRMS (ESI) $m/z$: $[M+Na]^+$ calcd for $C_{18}H_{18}O_4Na$ 321.1103, found 321.1105; IR: $\tilde{\nu}$ = 2945, 2871, 1735, 1679, 1576, 1447, 1370, 1340, 1189, 1008, 699 $cm^{-1}$; m.p. 99.5–100.7 °C.

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[9] CCDC 853124 (**4a**), CCDC 853123 (**5h**), and CCDC 853540 (**9b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

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