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A Convenient Route to Substituted Tetrahydrofuran-3-ones: Condensations of α-Bromo Ketones with Aromatic Aldehydes

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Abstract: *In the presence of K_2CO_3, α-bromo ketones react with aromatic aldehydes in methanol to produce substituted tetrahydrofuran-3-ones **3a-g** in good yields (55% to 83%). The reaction proceeds with initial formation of an α-ketoepoxide, followed by a tandem aldol reaction, cyclization and dehydration.*

Tetrahydrofuran-3-ones are attractive synthetic targets due to the number of natural compounds containing these substructures, such as *ascofuranone*,[2a] *glycinoeclepin A*,[2b] *norcembrenolides*[2c] and *chilenones A* and *B*.[2d] Synthetic approaches toward substituted furanones were well reviewed by Joullie and Semple in 1980.[3] A methodology involving condensation of 1,3-dithiane, epoxides and carbonyl compounds has also been reported.[4] More recent furanone synthesis include conversion of α-, β- or ω-alkoxy diazoketones via intramolecular rearrangements catalyzed by rhodium (II) acetate [5], and α-alkoxyorganosilanes or α-alkoxyorganostannanes via electrophilic capped carbonyl ylides.[6] Our interest in the synthesis of tetrahydrofuran-3-ones arose from the resolution of an impurity during our process development studies for a pharmaceutical intermediate. The experimental results suggested this impurity was directly derived from an α-bromo ketone and an aromatic aldehyde, and it was identified as a derivative of tetrahydrofuran-3-one. These laboratory observations and literature reviews prompted us to explore a potential new synthetic method for tetrahydrofuran-3-ones.

We present here our preliminary results on the preparation of substituted tetrahydrofuran-3-ones from readily available α-bromo ketones and aromatic aldehydes.[7] We also demonstrate that the essential synthetic intermediate is α-ketoepoxide for this condensation. This novel method allows for the direct construction of tetrahydrofuran-3-one under mild, basic conditions. We believe it provides an efficient and straightforward access to tetrahydrofuran-3-ones with potential synthetic applications.

α-Bromo ketones **1a-c** were easily prepared from the corresponding ketones following a known procedure.[8] As shown in Scheme I, condensations of α-bromo ketones **1a-c** (1 equiv.) with aromatic aldehydes **2a-e** (2 equiv.)) in the presence of K_2CO_3 (2 equiv.) in CH_3OH afforded tetrahydrofuran-3-ones **3a-g**.[9] All products were fully characterized spectroscopically (^{1}HNMR, ^{13}CNMR, IR and HRMS). The yields for these condensations, which were isolated and unoptimized, ranged from moderate to good (55% to 83%) based on the α-bromo ketones. The tetrahydrofuran-3-one obtained from this condensation possesses an unique structure with an *exocylic* double bond at C2 with *Z* configuration, a spiro-center at C4 and a racemic aromatic substitution at C5. This molecular structure was confirmed unambiguously by a single-crystal X-ray analysis of **3b** (R = cyclobutyl, Ar = *m*-nitrophenyl). Crystals of **3b** were obtained by crystallization from ethyl acetate, and the result of X-ray crystallographic analysis is depicted in Figure 1.

1 2 3

1a R = $(CH_3)_2CH$
1b R = $(CH_2)_3CH$
1c R = $(CH_2)_5CH$

2a Ar = m-$NO_2C_6H_4$
2b Ar = p-$NO_2C_6H_4$
2c Ar = p-BrC_6H_4
2d Ar = o-BrC_6H_4
2e Ar = p-CNC_6H_4

3a (67%, 1a + 2a), X = $C(CH_3)_2$
3b (75%, 1b + 2a), X = $C(CH_2)_3$
3c (55%, 1c + 2a), X = $C(CH_2)_5$
3d (80%, 1b + 2b), X = $C(CH_2)_3$
3e (68%, 1b + 2c), X = $C(CH_2)_3$
3f (76%, 1b + 2d), X = $C(CH_2)_3$
3g (83%, 1b + 2e), X = $C(CH_2)_3$

Scheme I: Preparation of Substituted Tetrahydrofuran-3-ones

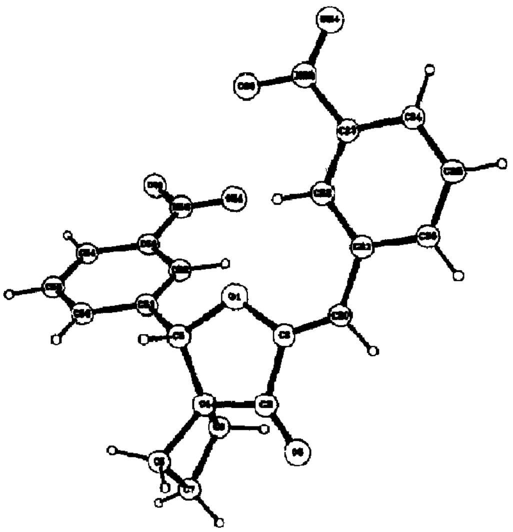
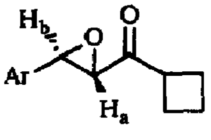


Figure 1: ***ORTEP*** **drawing of a molecule of 3b (racemic)**

Crystal data: $C_{20}H_{16}N_2O_6 \cdot 1/2C_4H_8O_2$, monoclinic, space group $C2/c$, a = 22.535 (3), b = 22.625 (3), c = 8.014 (3) Å, β = 105.83 (2)°, Z = 8, D_c = 1.434 g/cm^{-3}, μ(Cu $K\alpha$) = 8.64 cm^{-1}, R = 0.055, R_w = 0.063.

Our studies showed that suitable substrates for this condensation were aromatic aldehydes with *o*-, *m*- or *p*-electron-withdrawing groups, such as nitro, halogen and nitrile groups in aldehydes **2a-e**. For unsubstituted aromatic aldehyde (benzaldehyde) or aromatic aldehydes with electon-donating groups (*p*-anisaldehyde), reactions with **1b** were sluggish or failed to occur.

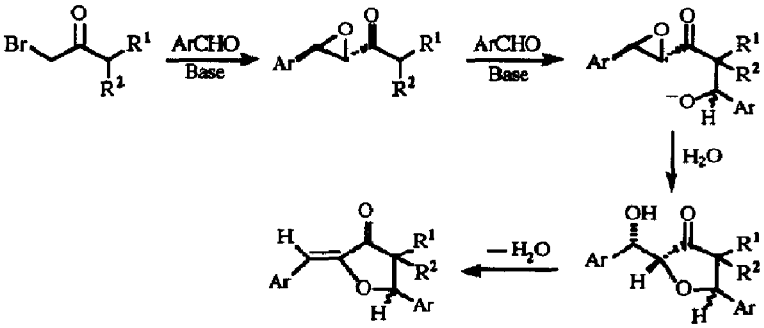
When the condensation between **1b** and **2a** was quenched after 2 h, an intermediate was isolated and its structure characterized as *trans*-α-ketoepoxide **4** ($J_{a,b}$ = 1.61 Hz).[10] The reaction of **4** with another equivalent of aldehyde **2a** resulted in furanone **3b** in 79% yield.



4

(Ar = *m*-Nitrophenyl)

On the basis of above observations, this condensation can be rationalized as a succession of *Darzen's condensation* between the α-bromo ketone and first equivalent of aldehyde to yield an α-ketoepoxide, then an *aldol reaction* between the α-ketoepoxide and a second equivalent of aldehyde, followed by *5-tet-exo cyclization* of the aldol adduct to release oxirane ring strain, which then forms tetrahydrofuranone ring. *Dehydration* under basic conditions then stereospecificaly introduces conjugated system (Scheme II).



Scheme II: Proposed Mechanism for Tetrahydrofuran-3-one

In summary, we have developed a convenient synthetic method for direct construction of highly substituted tetrahydrofuran-3-ones from two independent compounds under basic conditions. Construction of tetrahydrofuran ring, introduction of quaternary carbon and establishment of conjugated olefin with *Z* configuration were all achieved in a single synthetic operation. We also disclose the importance of α-ketoepoxides as synthetic intermediates for this condensation, which can be viewed as versatile synthetic precursors for tetrahydrofuran-3-ones.

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9. A typical procedure is as follows: A mixture of bromomethyl cyclobutyl ketone **1b** (0.89 g, 5.0 mmol) and 3-nitrobenzaldehyde **2a** (1.82 g, 12.0 mmol) in CH_3OH (10 ml) was stirred until all 3-nitrobenzaldehyde dissolved. To the stirring solution was added powdered K_2CO_3 (1.66 g, 12.0 mmol) as a single portion under N_2. The mixture was stirred at room temperature under N_2 and a precipitate formed slowly. After 60 h, H_2O (10 ml) was added to the reaction mixture and stirred for an hour. The resulting suspension was filtered through a funnel with medium porosity and washed with H_2O (3 x 10 ml). The solid was stirred in CH_3OH (15 ml) for 30 min. and was filtered again. The collected solid was dried *in vacuo* to afford **3b** (1.42 g, 1.90 g theor., 75%) as a pale-yellow solid: mp = 175-178 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.31-8.28 (m, 1H), 8.24 (s, 1H), 8.13 (dd, 1H), 8.04 (d, 1H), 7.69-7.67 (m, 2H), 7.53 (t, 1H), 6.52 (s, 1H), 5.66 (s, 1H), 2.65-2.55 (m, 1H), 2.35-2.15 (m, 2H), 2.13-2.04 (m, 1H), 1.81-1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.26, 148.60, 148.55, 147.68, 139.36, 135.65, 135.29, 132.17, 130.20, 129.60, 124.40, 123.80, 122.63, 121.35, 103.38, 88.22, 52.00, 29.54, 27.35, 15.48; IR (KBr) ν_{max} 1725, 1533, 1349 cm^{-1}; EIMS, *m/e* (relative intensity) 380 (M^+, 12), 352 (18), 189 (51), 172 (46), 163 (base), 89 (64); HRMS, *m/e* calcd. for $C_{20}H_{16}N_2O_6$ 380.1008, found 380.1005.
10. Spectral data for compound **4**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.92 Hz, 1H), 8.15 (s, 1H), 7.62 (d, J = 7.69 Hz, 1H), 7.57 (t, J = 7.92 Hz, 1H), 4.06 (d, J = 1.61 Hz, 1H), 3.45-3.54 (m, 2H), 2.28-2.42 (m, 2H), 2.15-2.28 (m, 2H), 2.01-2.11 (m, 1H), 1.86-1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 148.6, 137.8, 131.6, 129.9, 123.8, 120.7, 62.0, 56.8, 41.4, 24.2, 24.1, 18.1; IR (neat) ν_{max} 1705, 1535, 1218 cm^{-1}; EIMS, *m/e* (relative intensity) 247 (M^+, 7), 231 (5), 219 (23), 83 (39), 55 (100); HRMS, *m/e* calcd. for $C_{13}H_{13}NO_4$ 247.0845, found 247.0857.

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