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A Novel Three-Component Tetrahydrobenzofuran Synthesis

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Summary. Environment-friendly three component condensation reactions of cyclic 1,3-diketones, 4-nitrobenzaldehyde, and alkyl or aryl isocyanides to afford the corresponding tetrahydrobenzofuran derivatives in water in high yields within one hour are reported.

Keywords. Condensation reaction; Cyclic 1,3-diketone; Isocyanides; 4-Nitrobenzaldehyde; Tetrahydrobenzofuran.

Introduction

Tetrahydrobenzofurans fused with a six-membered ring at C_2–C_3 are an important class of heteroaromatic compounds that can be found as components of naturally occurring compounds [1]. They are also extensively utilized as synthetic intermediates in the preparation of a variety of natural products, such as evodone, pongamol, lanceolatin B, isoeupatin, tubipofurans, and paniculide A. Most of these have desirable medicinal properties and biological activities [1–6].

Several methods have been reported for the synthesis of tetrahydrobenzofurans [3, 4, 7–9], however, most of them rely on multi-step reactions and yields are low [3, 8, 9].

In connection with our previous work on the reaction of isocyanides with electron-deficient heterodienes [10–15] and synthesis of highly functionalized furans [10, 13, 15], we wish to report a facile and rapid protocol for the synthesis of tetrahydrobenzofurans by means of a three component condensation reaction of cyclic 1,3-diketones **1**, 4-nitrobenzaldehyde **2**, and alkyl or aryl isocyanides **3** in water at 75°C.

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Results and Discussion

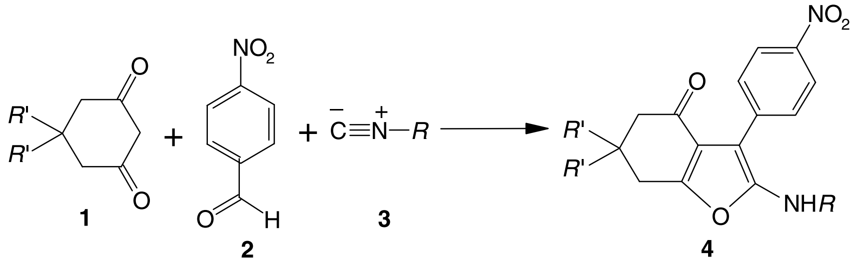
The one-pot three component condensation reactions of cyclic 1,3-diketones **1**, 4-nitrobenzaldehyde **2**, and alkyl or aryl isocyanides **3** proceeded spontaneously at 75°C in water and were complete within one hour (Scheme 1). ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of tetrahydrobenzofurans **4**. The structures of compounds **4a**–**4g** were deduced from their elemental analyses, IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m*/*z* values.

The ^{1}H NMR spectrum of **4a** exhibited four single sharp lines readily recognized as arising from two methyl ($\delta = 1.17$ ppm), *tert*-butyl ($\delta = 1.23$ ppm), and two methylene ($\delta = 2.39$ and 2.75 ppm) protons. A fairly broad singlet ($\delta = 3.81$ ppm) is observed for the NH group, and the 4-nitrophenyl moiety gave rise to characteristic signals in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 15 distinct resonances in agreement with the suggested structure. Partial assignment of these resonances is given in the Experimental.

The ^{1}H and ^{13}C NMR spectra of **4b**–**4g** are similar to those of **4a** except for the R and R′ groups, which exhibit characteristic signals with appropriate chemical shifts.

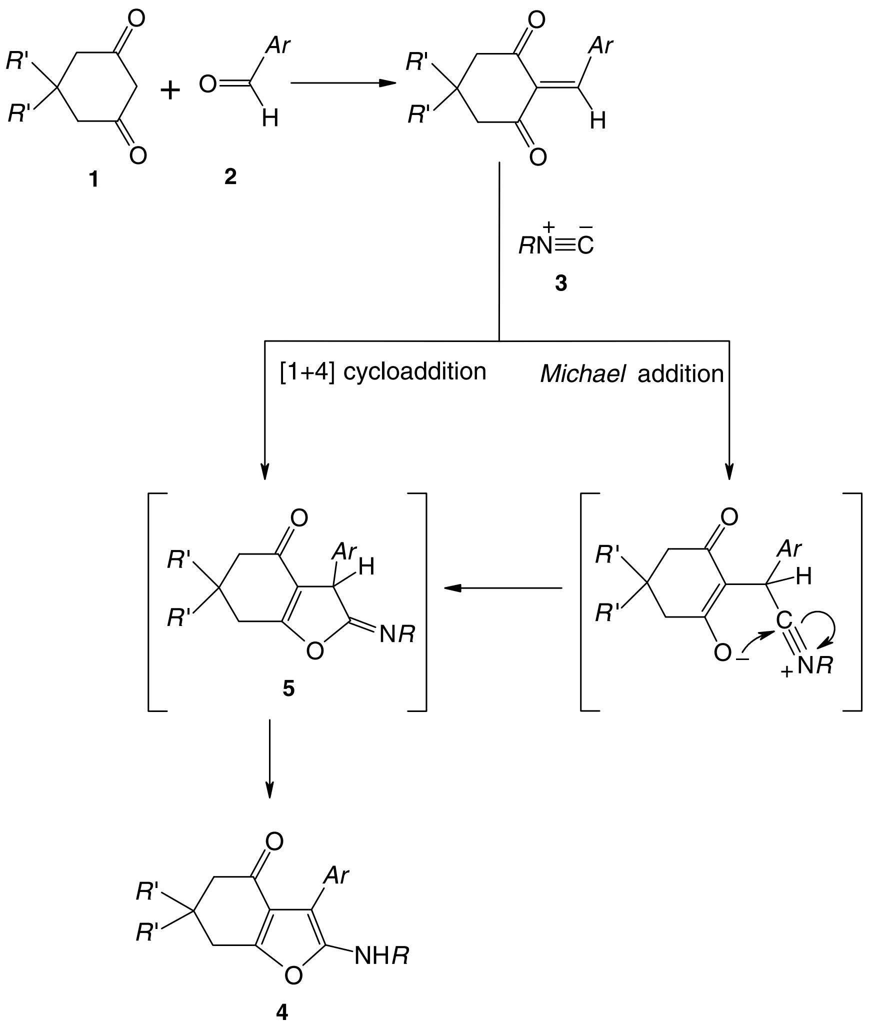
The synthesis of these tetrahydrobenzofurans can be rationalized by initial formation of a conjugated electron-deficient heterodiene by a *Knoevenagel* condensation [16] of the cyclic 1,3-diketones **1** and the aldehyde **2** followed by a [1 + 4] cycloaddition reaction [10–15, 17–20] or a *Michael*-type [21, 22] addition reaction with isocyanide **3** to afford an iminolactone **5**, which then isomerizes to yield the tetrahydrobenzofurans **4a**–**4g** (Scheme 2).

In conclusion, we have shown that the three-component condensation reactions of cyclic 1,3-diketones, 4-nitrobenzaldehyde, and alkyl or aryl isocyanides efficiently occurs in water without a catalyst at 75°C within one hour providing a



	R	*R'*
4a	*tert*-Butyl	CH_3
4b	Cyclohexyl	CH_3
4c	Benzyl	CH_3
4d	2,6-Dimethylphenyl	CH_3
4e	Cyclohexyl	H
4f	Benzyl	H
4g	2,6-Dimethylphenyl	H

Scheme 1



Scheme 2

convenient synthesis of substituted tetrahydrobenzofurans. The one-pot nature and the use of water as an eco-compatible reaction solvent makes it an interesting alternative reaction to two general multi-step approaches, namely (a) cyclic 1,3-diketone with alenic sulfonium salt followed by ene reaction with enophiles [7] and (b) diazocyclohexane-1,3-diones with vinyl acetate in the presence of rhodium catalyst followed by acid catalyzed dehydration [4].

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. These results were in full agreement with the calculated values. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.13 and 125.77 MHz. NMR spectra were obtained of solutions in $CDCl_3$ using *TMS* as internal standard. The *tert*-butyl, cyclohexyl, and 2,6-dimethylphenyl isocyanides used in this work were purchased from Fluka (Buchs, Switzerland) chemical company and the benzyl isocyanide was obtained from Aldrich chemical company.

Typical Procedure for the Preparation of ***4a***

To a magnetically stirred mixture of 0.155 g of 5,5-dimethyl-1,3-cyclohexanedione (1.1 mmol) and 0.151 g of 4-nitrobenzaldehyde (1.0 mmol) in 20 cm^3 of H_2O 0.084 g of *tert*-butyl isocyanide (1.0 mmol) were added *via* a syringe and heated for 1 h at 75°C. After cooling to room temperature, the resulting red precipitate was filtered off and washed with 50 cm^3 of H_2O. The solid was dried and crystallized from CH_2Cl_2:*Et*OH (1:2) to yield 0.253 g of **4a** as red crystals (71%).

2-(tert-Butylamino)-6,6-dimethyl-3-(4-nitrophenyl)-6,7-dihydro-1-benzofuran-4(5H)-one (**4a**, $C_{20}H_{24}N_2O_4$)

Mp 170–172°C; IR (KBr): $\bar{\nu}_{max} = 3390$ (N–H), 1664 (C=O), 1320 and 1505 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si): $\delta = 1.17$ (s, 2CMe_2), 1.23 (s, CMe_3), 2.39 (s, C=C–CH_2), 2.75 (s, O=C–CH_2), 3.81 (br s, NH), 7.62 and 8.19 (2d, $J = 8.7$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 28.55$ (2C*Me*$_2$), 30.32 (C*Me*$_3$), 34.91 (C=C–*C*H_2), 37.49 (O=C–*C*H_2), 52.84 (*C*Me_2), 54.07 (*C*Me_3), 103.04, 117.98, 123.40, 129.75, 139.72, 145.83, 153.42, and 160.83 (2C=C and $C_6H_4NO_2$), 193.47 (C=O) ppm; MS: $m/z(\%) = 356$ (M^+, 42), 300 (74), 244 (31), 216 (40), 57 (100), 41 (76).

2-(Cyclohexylamino)-6,6-dimethyl-3-(4-nitrophenyl)-6,7-dihydro-1-benzofuran-4(5H)-one (**4b**, $C_{22}H_{26}N_2O_4$)

Red crystals (0.298 g, 78%); mp 161–163°C; IR (KBr): $\bar{\nu}_{max} = 3395$ (N–H), 1666 (C=O), 1329 and 1497 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si): $\delta = 1.17$ (s, 2CMe_2), 1.19–1.99 (m, 5CH_2), 2.38 (s, C=C–CH_2), 2.73 (s, O=C–CH_2), 3.39 (m, N–CH), 4.07 (br s, NH), 7.59 and 8.17 (2d, $J = 8.5$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 24.86$, 25.49 and 34.17 (5CH_2), 28.56 (2C*Me*$_2$), 34.94 (C=C–*C*H_2), 37.36 (O=C–*C*H_2), 52.89 (*C*Me_2), 53.58 (N–CH), 95.81, 118.46, 123.58, 129.04, 140.01, 145.18, 154.00, and 159.46 (2C=C and $C_6H_4NO_2$), 193.61 (C=O) ppm; MS: $m/z(\%) =$ 382 (M^+, 100), 300 (23), 244 (15), 216 (21), 83 (10), 55 (49), 41 (37).

2-(Benzylamino)-6,6-dimethyl-3-(4-nitrophenyl)-6,7-dihydro-1-benzofuran-4-(5H)-one (**4c**, $C_{23}H_{22}N_2O_4$)

Red crystals (0.285 g, 73%); mp 108–110°C; IR (KBr): $\bar{\nu}_{max} = 3410$ (N–H), 1668 (C=O), 1316 and 1492 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si): $\delta = 1.16$ (s, 2CMe_2), 2.37 (s, C=C–CH_2), 2.72 (s, O=C–CH_2), 4.41 (s, CH_2Ph), 4.60 (br s, NH), 7.27–7.35 (m, C_6H_5), 7.52 and 8.11 (2d, $J = 8.4$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 28.53$ (C*Me*$_2$), 34.94 (C=C–*C*H_2), 37.29 (O=C–*C*H_2), 48.80 (CH_2Ph), 52.85 (*C*Me_2), 95.85, 118.61, 123.52, 127.62, 127.80, 128.81, 129.12, 138.38, 139.58, 145.29, 153.96, and 159.50 (2C=C, $C_6H_4NO_2$, and C_6H_5), 193.68 (C=O) ppm; MS: $m/z(\%) = 390$ (M^+, 63), 299 (5), 91 (100).

2-(2,6-Dimethylphenylamino)-6,6-dimethyl-3-(4-nitrophenyl)-6,7-dihydro-1-benzofuran-4(5H)-one (**4d**, $C_{24}H_{24}N_2O_4$)

Orange crystals (0.288 g, 71%); mp 224–226°C; IR (KBr): $\bar{\nu}_{max} = 3270$ (N–H), 1653 (C=O), 1498 and 1328 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si): $\delta = 1.14$ (s, CMe_2), 2.16 (s, C_6H_3*Me*$_2$), 2.38 (s, C=C–CH_2), 2.66 (s, O=C–CH_2), 5.75 (br s, NH), 6.96–7.00 (m, C_6H_3), 7.63 and 8.07 (2d, $J = 7.8$ Hz,

$C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 18.42$ (C_6H_3*Me*$_2$), 28.46 (C*Me*$_2$), 34.92 (C=C–*C*H_2), 37.37 (O=C–*C*H_2), 52.86 (*C*Me_2), 99.25, 118.50, 123.05, 125.10, 128.84, 129.49, 132.10, 136.77, 138.85, 145.49, 150.60, and 160.31 (2C=C, $C_6H_4NO_2$, and C_6H_3), 193.57 (C=O) ppm; MS: m/z (%) = 405 (MH^+, 100), 305 (10), 172 (12), 105 (29), 77 (43), 41 (32).

2-(Cyclohexylamino)-3-(4-nitrophenyl)-6,7-dihydro-1-benzofuran-4(5H)-one
(**4e**, $C_{20}H_{22}N_2O_4$)

Red crystals (0.298 g, 84%); mp 153–155°C; IR (KBr): $\bar{\nu}_{max} = 3420$ (N–H), 1654 (C=O), 1502 and 1323 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si): $\delta = 1.17$–1.98 (m, 5CH_2), 2.18 (m, O=C–CH_2–C*H*$_2$), 2.48 (t, $J = 6.3$ Hz, C=C–CH_2), 2.85 (t, $J = 6.0$ Hz, O=C–CH_2), 3.40 (m, N–CH), 4.10 (br s, NH), 7.56 and 8.15 (2d, $J = 8.2$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 22.34$ (C=C–CH_2–*C*H_2), 23.36 (C=C–*C*H_2), 24.86, 25.50 and 34.13 (5CH_2), 38.49 (O=C–*C*H_2), 53.50 (N–CH), 95.76, 119.70, 123.51, 129.15, 140.08, 145.18, 153.73, and 160.43 (2C=C and $C_6H_4NO_2$), 194.13 (C=O) ppm; MS: m/z (%) = 354 (M^+, 75), 272 (81), 255 (18), 83 (32), 55 (100), 41 (71).

2-(Benzylamino)-3-(4-nitrophenyl)-6,7-dihydro-1-benzofuran-4(5H)-one
(**4f**, $C_{21}H_{18}N_2O_4$)

Red crystals (0.294 g, 81%); mp 119–121°C; IR (KBr): $\bar{\nu}_{max} = 3372$ (N–H), 1642 (C=O), 1492 and 1324 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si): $\delta = 2.18$ (m, O=C–CH_2–C*H*$_2$), 2.48 (t, $J = 6.1$ Hz, C=C–CH_2), 2.85 (t, $J = 6.0$ Hz, O=C–CH_2), 4.42 (s, N–CH_2), 4.52 (br s, NH), 7.27–7.35 (m, C_6H_5), 7.51 and 8.13 (2d, $J = 8.3$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 22.32$ (C=C–CH_2–*C*H_2), 23.30 (C=C–*C*H_2), 38.47 (O=C–*C*H_2), 48.74 (N–CH_2), 95.79, 119.85, 123.53, 127.58, 127.80, 128.83, 129.21, 138.38, 139.60, 145.36, 153.60, and 160.37 (2C=C, $C_6H_4NO_2$, and C_6H_5), 194.14 (C=O) ppm; MS: m/z (%) = 362 (M^+, 2), 256 (10), 150 (27), 91 (100).

2-(2,6-Dimethylphenylamino)-3-(4-nitrophenyl)-6,7-dihydro-1-benzofuran-4(5H)-one
(**4g**, $C_{22}H_{20}N_2O_4$)

Orange crystals (0.275 g, 73%); mp 172–173°C; IR (KBr): $\bar{\nu}_{max} = 3225$ (N–H), 1654 (C=O), 1504 and 1329 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si): $\delta = 2.16$ (s, 2CH_3), 2.17 (m, O=C–CH_2–C*H*$_2$), 2.50 (t, $J = 6.7$ Hz, C=C–CH_2), 2.79 (t, $J = 6.2$ Hz, O=C–CH_2), 5.68 (br s, NH), 6.98–7.01 (m, C_6H_3), 7.60 and 8.09 (2d, $J = 8.3$ Hz, $C_6H_4NO_2$) ppm; ^{13}C NMR ($CDCl_3$, Me_4Si): $\delta = 18.43$ (C_6H_3*Me*$_2$), 22.25 (C=C–CH_2–*C*H_2), 23.39 (C=C–*C*H_2), 38.48 (O=C–*C*H_2), 98.78, 119.75, 123.06, 125.34, 128.79, 129.55, 132.49, 136.56, 138.87, 145.58, 150.35, and 161.09 (2C=C, $C_6H_4NO_2$, and C_6H_5), 194.06 (C=O) ppm; MS: m/z (%) = 376 (M^+, 70), 256 (10), 172 (10), 131 (100), 105 (50), 77 (83), 55 (79).

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References

[1] Hou XL, Cheung HY, Hon TY, Kwan PL, Lo TH, Tong SY, Wong HNC (1998) Tetrahedron **54**: 1955
[2] Jacobi PA, Walker DJ, Odeh IMA (1981) J Org Chem **46**: 2065
[3] Pirrung MC, Zhang J, Morehead AT Jr (1994) Tetrahedron Lett **35**: 6229
[4] Pirrung MC, Lee YR (1994) Tetrahedron Lett **35**: 6231

[5] Ojida A, Tanoue F, Kanematsu K (1994) J Org Chem **59**: 5970
[6] Jacobi PA, Kaczmarek SR, Udodong UE (1984) Tetrahdron Lett **25**: 4859
[7] Ojida A, Abe A, Kanematsu K (1994) Heterocycles **38**: 2585
[8] Ogawa T, Murafuji T, Iwata K, Suzuki H (1989) Chem Lett 325
[9] Lévai A, Kočevar M, Tóth G, Simon A, Vraničar L, Adam W (2002) Eur J Org Chem 1830
[10] Shaabani A, Teimouri MB, Bijanzadeh HR (2002) Tetrahedron Lett **43**: 9151
[11] Shaabani A, Teimouri MB, Bijanzadeh HR (2002) J Chem Res(S) 433
[12] Shaabani A, Yavari I, Teimouri MB, Bazgir A, Bijanzadeh HM (2001) Tetrahedron **57**: 1375
[13] Shaabani A, Ajabi S, Farrokhzad F, Bijanzadeh HM (1999) J Chem Res(S) 582
[14] Shaabani A, Farrokhzad F (1997) J Chem Res(S) 344
[15] Yavari I, Shaabani A, Maghsoodlou MT (1997) Monatsh Chem **128**: 697
[16] Tu S, Zhou J, Lu Z, Deng X, Shi D, Wang S (2002) Synth Commun **32**: 3063
[17] Buron C, Kaïm LE, Usla A (1997) Tetrahedron Lett **38**: 8027
[18] Marchand E, Morel G, Sinbandhit S (1999) Eur J Org Chem 1729
[19] Morel G, Marchand E, Sinbandhit S, Carlier R (2001) Eur J Org Chem 655
[20] Nair V, Menon RS, Vinod AU, Viji S (2002) Tetrahedron Lett **43**: 2293
[21] Bednar R, Haslinger E, Herzig U, Polansky OE, Wolschann P (1976) Monatsh Chem **107**: 1115
[22] Liedl E, Wolschann P (1982) Monatsh Chem **113**: 1067