Tribenzoyldihydropyridinols from dibenzoylacetylene and imines

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The reaction of dibenzoylacetylene with *N,N'*-dialkyl or *N,N'*-diaryl glyoxal-bisimnes or with benzylideneanilines in boiling ethanol leads to the formation of pentasubstituted 1,2-dihydropyridines in 52–87 % yield together with the corresponding enamines derived from dibenzoylacetylene.

Keywords: pyridine, glyoxal-bisimines, benzylideneanilines, dibenzoylacetylene, enamines, imines

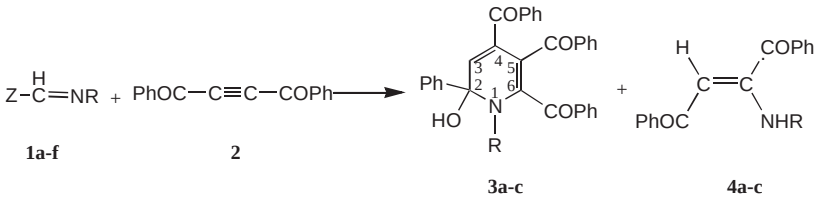
Some years ago the behaviour of dibenzoylacetylene **2** with diarylacetamidines was investigated and 4-phenylpyridin-2-one derivatives could be prepared.[1] Earlier, it had been reported that benzoylphenylacetylene (1,3-diphenyl-2-propyn-1-one) reacted with *N*-arylacetamides to yield the corresponding 2-pyridones.[2] In both cases the reactions underwent Michael addition type reaction followed by ring closure. When dibenzoylacetylene was reacted with 2-anilino-1-phenylethanone a 2,3-dibenzoyl-1,4-diphenylpyrrole was formed.[3] *o*-Substituted anilines like 2-cyanoaniline condensed with dibenzoylacetylene to give 2,3-dibenzoyl-4-imino-1,4-dihydroquinoline along with the corresponding enamine,[4] while with 2-acetyl- and 2-benzoyl-aniline the dibenzoylacetylene gave the corresponding 1,3-dibenzoyl-4-methyl- or -4-phenyl-quinoline.[4] Recently it has been reported that the reaction of dibenzoylacetylene and enol systems, such as acetylacetone, 5,5-dimethylcyclohexane-1,3-dione, 1-naphthol, 2-naphthol, 2,7-dihydroxynaphthalenes, or 8-hydroxyquinoline, in the presence of triphenylphosphine, leads to tetrasubstituted furans.[5]

The goal of the present work was a systematic study of the preparation of pyrazines or pyridines through [4+2]-cycloaddition reactions, but we obtained instead the hydroxypyridines. So in this communication we report a preliminary investigation of an unexpected and efficient synthetic route to polysubstituted pyridines **3a**–**c** using dibenzoylacetylene **2** and the imines **1a–f**. Thus, the reaction between **1a–f** and **2** in ethanol leads to the highly functionalized hydroxypyridines **3a–c** in 52–87 % yield (Table 1), together with the corresponding enamines **4a–c**[6-8] (only in cases of reaction **1d–f** with **2**) (Scheme 1).

The structures of compounds **3a–c** were deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **3a** exhibited three singlets identified as methyl (δ = 2.30), 3-H of the pyridine ring (δ = 6.26) and a hydroxyl group (δ = 12.54) along with multiplets (δ = 6.85–7.41) for the aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum showed 29 distinct resonances in agreement with the proposed structure. ^{13}C DEPT showed also one characteristic peak at δ = 86.4 for the quaternary carbon atom C-2, a doublet at δ = 124.6 for C-3 and three quaternary carbon atoms at low field, at δ = 192.4, 193.0, 195.0 for the three carbonyl groups. Thus the number of signals attributable to quaternary carbonyl carbon atoms excludes the open structure **7a–c** (Scheme 2) and supports cyclic structure **3a-c**. All six cyclohexyl carbon atoms appeared in the ^{13}C NMR spectrum of compound **3c**: this can be attributed to restriction of rotation, on account of the greater steric bulk of the saturated ring, compared with that of benzene in **3a**, **b**, where the *ortho* and *meta* carbon pairs were isochronous under the conditions of the NMR experiment.

Table 1 Reaction of imines **1a–f** with dibenzoylacetylene **2** (Scheme 1)

Entry	Imine	Z	R	Product	Yield/%
1	**1a**	4-$Me_2NC_6H_4$	4-MeC_6H_4	**3a**	87
2	**1b**	4-$Me_2NC_6H_4$	4-$MeOC_6H_4$	**3b**	77
3	**1c**	4-$Me_2NC_6H_4$	C_6H_{11}	**3c**	68
4	**1d**	CH=N(C_6H_4-4-Me)	4-MeC_6H_4	**3a**	52
5	**1e**	CH=N(C_6H_4-4-OMe)	4-$MeOC_6H_4$	**3b**	71
6	**1f**	CH=NC_6H_{11}	C_6H_{11}	**3c**	63



a: Z = 4-$Me_2NC_6H_4$, R = 4-MeC_6H_4

b: Z = 4-$Me_2NC_6H_4$, R = 4-$MeOC_6H_4$

c: Z = 4-$Me_2NC_6H_4$, R = C_6H_{11}

d: Z = CH=N(C_6H_4-4-Me), R = 4-MeC_6H_4

e: Z = CH=N(C_6H_4-4-OMe), R = 4-$MeOC_6H_4$

f: Z = CH=NC_6H_{11}, R = C_6H_{11}

a: R = 4-MeC_6H_4

b: R = 4-$MeOC_6H_4$

c: R = C_6H_{11}

Scheme 1

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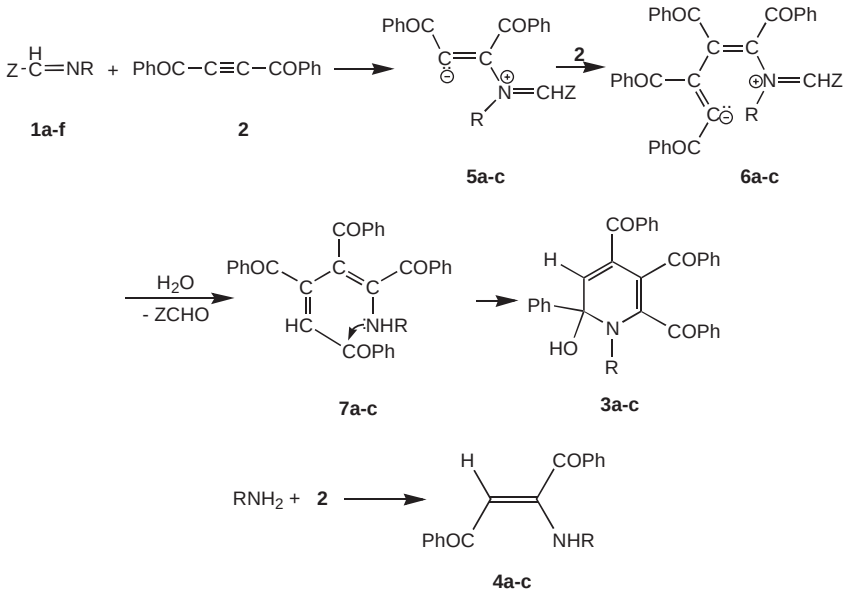

Z = 4-$Me_2NC_6H_4$, CH=N(4-MeC_6H_4), CH=N(4-$MeOC_6H_4$), or CH=NC_6H_{11}

R = 4-MeC_6H_4, 4-$MeOC_6H_4$, C_6H_{11}

Scheme 2

Formation of pyridines **3a–c** may be rationalised as an initial nucleophilic addition of the imine **1a–f** to dibenzoylacetylene **2** to give **5a–c** followed by subsequent addition to another molecule of dibenzoylacetylene to give **6a–c**. The latter undergoes hydrolysis by water[1] to give the enamine **7a–c** (together with the corresponding iminoglyoxal or aldehyde) which undergoes ring closure to produce the hydroxy-1,2-dihydropyridines **3a–c**. The iminoglyoxal also undergoes hydrolysis to give the glyoxal and the free amine which adds to another molecule of dibenzoylacetylene to form the corresponding enamine **4a–c**[6-8] (Scheme 2).

In summary: a one-step synthesis of polysubstituted 6-hydroxy-1,2-dihydropyridines from readily available starting materials benzylideneanilines or glyoxal-bisimines is disclosed.

Experimental

The uncorrected melting points were determined on a Griffin & George apparatus. Elemental analyses were carried out by Microanalysis Centre at Cairo University. The IR spectra (KBr) were recorded on a Shimadzu 470 spectrophotometer. The 300 and 400MHz ^{1}H NMR, 75 and 100MHz ^{13}C NMR spectra were observed on a Bruker WM 300 and AM 400 spectrometer. The MS (70eV, EI mode) were recorded on a Jeol JMS600 instrument. Preparative layer chromatography (plc) used air dried 1.0 mm thick layers of slurry applied silica gel Merck PF_{254} on 48 × 20 cm glass plates and toluene-ethyl acetate (2:1) as developing solvent. Zones were detected by the colour or by quenching of indicator fluorescence upon exposure to 254 nm UV light and eluted with acetone. Reactions were monitored by TLC.

Starting materials: Benzylideneanilines **1a–c**[9], *N,N'*-diaryl glyoxal-bismines **1d,e**[10], *N,N'*-dicyclohexyl glyoxal-bismines **1f**[11] and dibenzoylacetylene **2**[12] were prepared according to literature procedures.

Preparation of compounds **3a–c**: Dibenzoylacetylene (234 mg, 1.0 mmol) was added to the imine **1a–f** (0.5 mmol) in ethanol (10 ml) and the solution was refluxed for 10h. Then the reaction mixture was evaporated *in vacuo* and the residue was subjected to TLC using toluene/ethyl acetate 10:1. The fastest zones contained the enaminoketones **4a–c** while the slowest contained the pyridines **3a–c**. The products were recrystallised from the indicated solvents.

4,5,6-Tribenzoyl-2-hydroxy-1-(4-methylphenyl)-2-phenyl-1,2-dihydropyridine (**3a**): yellow crystals, m.p. 174–175°C (ethanol). ^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H, CH_3), 6.26 (s, 1H, 3-H), 6.85–7.41 (m, 24H, Aryl-H), 12.54 (s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ = 21.0 (CH_3), 86.4 (C-2), 109.0, 120.3, 124.6 (C-3), 125.7, 127.2, 127.6, 127.8, 128.2, 128.3, 128.5, 128.7, 129.2, 130.4, 132.0 and 133.3 (all aryl-*C*H) 130.1, 131.7, 133.5, 136.9, 137.2, 137.3, 138.9, 140.5, 152.55, 192.4, 193.0, 195.0 (quat. *C*), IR (KBr): ν = 3450 (OH), 1660 (C=O) cm^{-1}. MS: *m/z* (%) = 575 (M^+, 3), 573(3), 543 (5), 469 (15), 453(35), 438 (20), 424 (16), 105 (100), 77(46). Anal.Calcd for $C_{39}H_{29}NO_4$ (575.7): C, 81.37; H, 5.08; N, 2.43. Found: C, 81.22; H, 5.01, N, 2.31 %.

4,5,6-Tribenzoyl-2-hydroxy-1-(4-methoxyphenyl)-2-phenyl-1,2-dihydropyridine (**3b**): yellow crystals, m.p. 195–196°C (ethanol); ^{1}H NMR (DMSO-d_6): δ = 3.60 (s, 3H, OCH_3), 6.48 (s, 1H, 3-H), 6.51 (s, 1H, OH); 6.67–7.67 (m, 24H, Aryl-H); ^{13}C NMR (DMSO-d_6): δ = 55.4 (CH_3O), 85.1 (C-2), 107.7, 113.7, 124.8 (C-3), 125.7, 127.3, 127.4, 127.7, 127.9, 128.1, 128.2, 128.3, 128.7, 130.7, 131.3 and 133.0 (all aryl-*C*H) 128.6, 129.3, 129.4, 134.8, 136.9, 137.7, 138.8, 140.2, 156.9, 189.6, 190.1, 193.5 (quat. *C*); IR (KBr): ν = 3445 (OH), 1655 (C=O) cm^{-1}. IR (KBr): MS: *m/z* (%) = 591 (M^+, 4), 559(4), 485 (19), 469 (37), 452 (25), 440 (10), 105 (100), 77 (45). Anal.Calcd for $C_{39}H_{29}NO_5$ (591.7): C, 79.17; H, 4.94; N, 2.37. Found: C, 78.93; H, 4.98, N, 2.55 %.

4,5,6-Tribenzoyl-1-cyclohexyl-2-hydroxy-2-phenyl-1,2-dihydropyridine (**3c**): yellow crystals, m.p. 155–156°C (ethanol). ^{1}H NMR (DMSO-d_6): δ = 0.54–1.98 (m, 10H, cyclohexyl-CH_2), 3.98 (m, 1H, cyclohexyl-CH), 6.91–7.54 (m, 21H, 3-H and phenyl-H), 10.72 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ = 23.8, 24.1, 24.3, 32.4 and 32.8 (5 cyclohexyl-CH_2), 52.3 (cyclohexyl-*C*H), 84.1 (C-2), 105.4, 124.5 (C-3), 126.7 127.1, 127.3, 127.4, 127.5, 127.6, 127.9, 128.3, 128.7, 129.7, 130.6 and 133.8 (all aryl-*C*H), 134.4, 136.3, 139.0, 140.1, 140.4, 153.2, 189.7, 190.7, 192.7 (quat. *C*); IR (KBr): ν = 3442 (OH), 1658 (C=O) cm^{-1}. MS: *m/z* (%) = 567 (M^+, 27), 559 (4), 462 (36), 446 (37), 105 (100), 56 (46). Anal.Calcd for $C_{38}H_{33}NO_4$ (567.7): C, 80.40; H, 5.86; N, 2.47. Found: C, 80.33; H, 5.78, N, 2.40 %.

(Z)-2-(4-Methylphenylamino)-1,4-diphenylbut-2-ene-1,4-dione (**4a**): yellow crystals (0.08 g, 24 %), m.p. 139–140°C (lit.[6] 142°C).

(Z)-2-(4-Methoxyphenylamino)-1,4-diphenylbut-2-ene-1,4-dione (**4b**): yellow crystals (0.075 g, 21 %), m.p. 119–120°C (lit.[7] 121–122°C).

(Z)-2-Cyclohexylamino-1,4-diphenylbut-2-ene-1,4-dione (**4c**): yellow crystals (0.07 g, 21%), m.p. 129–130°C (lit.[8] 130–132°C).

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References

1 M.A.-M. Gomaa, *J. Chem. Res. (S)* 1997, 444; *J. Chem. Res. (M)*, 1997, 2679.
2 N.R. El-Rayyes and F.H. Al-Hajjar, *J. Heterocycl. Chem*., 1984, **21**, 1473.

3 S. Lahiri, M.P. Mahajan, R. Prasad and M.V. George, *Tetrahedron*, 1977, **33**, 3159.
4 M.S. Sinsky and R.G. Bass, *J. Heterocycl. Chem*., 1984, **21**, 759.
5 I. Yavari, M. Anary-Abbasinejad and A. Alizadeh, *Tetrahedron Lett.*, 2003, **43**, 4503.
6 E. Jolles, *Gazz. Chem. Ital.*, 1938, **68**, 488.
7 E. Van Loock, G. L'abbé and G. Smets, *Tetrahedron Lett.*, 1970, **20**, 1693.
8 A.B. Turner, H.W. Heine, J. Irving and J.B.Bush, Jr, *J. Am. Chem. Soc*., 1965, **87**, 1050.
9 A. Roe and J.A. Montgomery,. *J. Am. Chem. Soc*., 1952, **75**, 910.
10 J.M. Kliegman and R.K. Barnes, *J. Org. Chem*., 1970, **35**, 3140.
11 J.M. Kliegman and R.K. Barnes, *Tetrahedro*n, 1970, **26**, 2555.
12 A.I. Nogideli, K. Tsiskarishvili and A. Beshidze, *Sbornik State Obshchei Khim*., 1953, **2**, 1639; *Chem. Abstr.* **49**, 5401i.