

FACILE PREPARATION OF DEOXYBENZOINS VIA A NOVEL SYNTHESIS OF ENAMINES

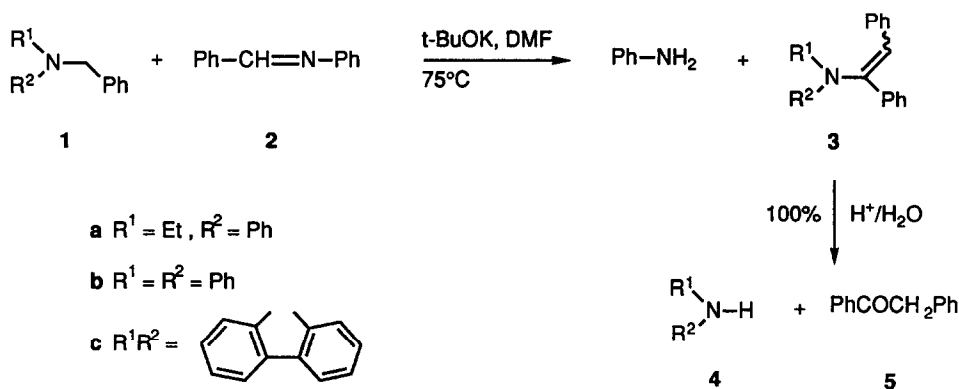
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ABSTRACT: N-Aryl(or alkyl)-N-benzylanilines and benzyldineaniline condense in N,N-dimethylformamide in the presence of potassium t-butoxide to give enamines in good yields. Hydrolysis of the latter give deoxybenzoin with 100% conversion.

Acyclic enamines are most conveniently synthesized by the reaction of ketones or aldehydes with dialkylamines.¹ The synthetic applications pioneered by Stork² have been the focus of much work.¹ Herein we report a new class of enamines **3** prepared from tertiary amines **1** and the imine **2** in N,N-dimethylformamide using potassium *tert*-butoxide as a catalyst (Scheme 1). Examples of these reactions are shown in the Table. In this novel reaction the activated methylene carbon of the benzyl group condenses with the methylene carbon of

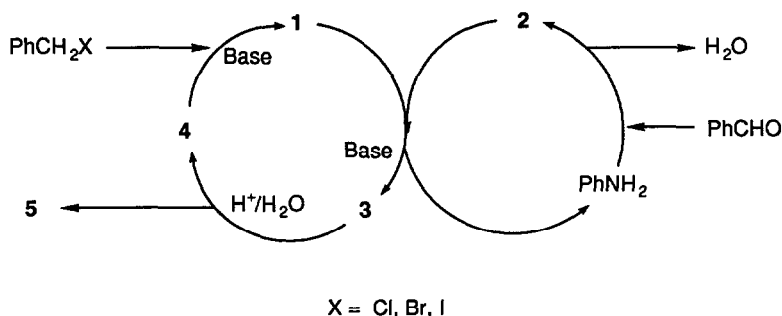
Scheme 1



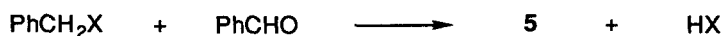
2 to give a carbon-carbon double bond with elimination of aniline. This chemistry is similar to the formation of stilbenes from the reaction of aromatic Schiff's bases with methyl-substituted aromatic and heteroaromatic rings as reported by Siegrist.³

Scheme 2 shows a catalytic cycle for the production of deoxybenzoin. Formation of the enamines releases aniline which may be recycled by condensation with benzaldehyde to produce more imine **2**. Hydrolysis of the enamines, **3**, gives the ketone **5** and the secondary amines **4** which are easily separated. The latter when reacted with halomethylbenzene give the tertiary amines **1** and the cycle resumes. Thus the overall equation for

Scheme 2



the novel synthesis of **5** may be written as:



Compound **1a** was a commercial product (Aldrich). The tertiary amine **1b**⁴ was obtained in 89% yield from the reaction of diphenylamine (10 mmol) and benzyl chloride (26 mmol) in toluene (20 mL) containing powdered⁵ KOH/K₂CO₃ (60:16 mmol) and tetrabutylammonium hydrosulfate (1 mmol)⁶ at 72 °C for 45 min or in ~100% yield from benzyl phenyl ether and **2**.⁷ The 9-benzylcarbazole (**1c**)⁸ was synthesized (92% yield) following the phase-transfer catalytic procedure used for **1b** but employing only a 10% excess of benzyl chloride.

A typical preparation of the enamines (**3**)⁹ follows. Diphenylbenzylamine **1b** (3.92 g, 15.1 mmol) and N-phenylbenzaldimine (**2**) (3.0 g, 16.5 mmol) were heated for 150 min in DMF (50 mL) containing t-BuOK (5.6 g, 50 mmol) under a slow stream of nitrogen. Based on reversed phase HPLC results, after 150 min the conversion of **1b** was 94%. From a calibration graph the yield of the enamine was 75%. This material was isolated by pouring the organic solution into H₂O (150 mL) and filtering the precipitate. The sticky solid was treated with activated charcoal in boiling MeOH filtered and cooled. The enamine crystallized slowly as pale green-yellow prisms (recovered yield 60%).

The enamine derived from carbazole is produced in better yields and within a shorter period (see Table) probably due to the enhanced acidity of the methylene hydrogens.¹⁰ This reaction was used to probe both the solvent and the base used when the amounts of the reactants **1c** (5 mmol) and **2** (7.5 mmol) were kept constant at 75°C in DMF (50 mL) under N₂ atmosphere. For the reactions listed in the Table the DMF used contained 0.15% water. Utilizing this solvent in four experiments where the amount of t-BuOK varied from 2-50 mmol and the reaction was run for up to 20 min, the yields of **3c** after recrystallization ranged from 72-81% except for the experiment run with 2 mmol of t-BuOK where the reaction was slow and the yield of **3c** was <5% (not recovered). However, when the DMF was dried¹¹, two experiments using 0.89 and 2.3 mmol of t-BuOK in

which the reactions were worked up after 10 min gave identical yields of **3c** (81%) which demonstrates that the reaction is catalytic with respect to the base. Using sodium dimethylamide produced *in situ* from DMF and metallic sodium (50 mL: 1 g)⁷ a 58% yield of recrystallized **3c** was isolated after 20 min. With sodium methoxide (53 mmol) in dry DMF (50 mL) no enamine (**3c**) was obtained after 43 min.

The hydrolysis on a one-gram scale of the enamines **3a,b** was easily carried out in a mixture of THF (30 mL) and 1.2 M HCl (7 mL) by heating under reflux for 1 h. The solution was neutralized (Na₂CO₃), filtered and the solvents evaporated. N-Ethylaniline may be easily separated from the resulting mixture by dissolving in chloroform and extracting with 1.2 M HCl. The organic layer after drying (Na₂SO₄) was evaporated and the residue recrystallized from petroleum ether 35-60°C (abbreviated elsewhere as PE) to give deoxybenzoin¹² in quantitative yield.

N,N-Diphenylamine from the hydrolysis of **3b** was separated from the ketone as a first fraction by chromatography (PE/benzene/EtOAc 90:9:1). The fractions containing the ketone **5** were combined, the solvent evaporated and the residue recrystallized from PE. The recovery of **5** was 80% of theory.

Under the same conditions for the hydrolysis of **3a** and **b**, **3c** can be recovered unchanged after 24 h under reflux. It was expected from the behaviour of similar enamines¹³ that the hydrolysis of the more substituted carbazole enamines would be slower. By changing the solvent mixture to acetic acid (18 mL) containing 6 M HCl (2 mL)¹⁴ and heating under reflux for 5 h the enamine **3c** is completely hydrolyzed. Upon cooling about 80% of the carbazole crystallized out and was removed by filtration. The residue obtained after workup as for **3a** and **b** was treated with boiling PE (3x30 mL) which extracts the ketone almost exclusively. The solutions were combined, filtered and the volume was reduced to 50 mL. Upon cooling the ketone **5** crystallized and was recovered in ~80% yield.

The research is continuing on the novel enamines obtained by this general method focusing on the preparation of substituted deoxybenzoin which can be easily oxidized to tetraketones and used for the preparation of high-temperature thermo-oxidatively stable polymers.

Table: The Reaction of Tertiary Amines (1) with Benzaldehyde Anil (2).^a

Reactants Ratio 1(mmol) : 2(mmol)	Enamine 3	Time (min)	Conversion of amine 1 (%)	Yield ^b (%)	mp(°C)(solvent)
a (10) : (12)	a	120	- ^c	67 ^d	oil ^d
b (15) : (16.5)	b	150	94	75 ^e	85-87 (MeOH)
c (10) : (10)	c	5	100	81 ^f	160-162 (EtOAc/MeOH)

^aReaction employed t-BuOK/DMF (50 mmol: 50 mL) at 75°C under N₂ atmosphere. ^bNot optimized. From calibration curve of pure product and HPLC reaction mixture. ^cAmine did not show a peak on HPLC. ^dAfter flash chromatography on silica-60 (PE/CHCl₃ 9:1). Recovered material ~61%. ^ePrecipitate (see typical reaction) may be recrystallized directly, but an analytical sample was chromatographed (PE/CHCl₃ 9:1) and recrystallized. ^fCalculated after one recrystallization.

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References and Notes

- References and examples can be found in the reviews: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975; *ibid.* **1982**, *38*, 3363; *ibid.* **1984**, *40*, 2989.
- Stork, G; Terrell, R.; Szmuszkowicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029.
- For review see: Fletcher, I. J.; Siegrist, A. E. *Adv. Heterocycl. Chem.* **1978**, *23*, 171.
- 1b**: mp 88-89°C (lit^{a,b} 88-89°C). a) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1984**, *106*, 3234. b) Eisch, J. J.; Dua, S. K.; Kovacs, C. A. *J. Org. Chem.* **1987**, *52*, 4437.
- Powdering and mixing in toluene was effected with a Janke and Kunkel Ultra-turrax T25 blender.
- The conditions for PTC were chosen on the basis of published results on the alkylation of amines with butyl bromide: Dehmlow, E. V.; Lipka, B. *J. Chem. Res., Synop.* **1985**, 107.
- The medium used for its preparation is a mixture of metallic Na and DMF prepared as outlined: Paventi, M.; Hay, A. S. *Synthesis* **1990**, 878. The novel preparation of **1b** has been submitted to *J. Org. Chem.*
- 1c**: mp 117-119°C (118-119°C, Nishi, H.; Kohno, H.; Kano, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1897).
- Physical data for the enamines follows. **3a**: ¹H NMR (200 MHz, CDCl₃) δ 1.25 (t, 3H, J= 4.8 Hz, CH₃), 3.55 (q, 2H, NCH₂CH₃), 6.77-6.81 (m, 4H), 7.11-7.54 (m, 12H); IR (CDCl₃) 3083 (w), 3063, 3028, 2975, 2935 (w), 2873 (w), 1598 (s), 1574, 1500 (s), 1497 (s), 1462 (w), 1448, 1392, 1378, 1340, 1318 (w), 1295 (w), 1271, 1243 (w), 1208 (w), 1161, 1122, 1076 (w), 1032, 1008 (w) cm⁻¹; MS (EI) *m/e* calc'd for C₂₂H₂₁N: 299.167, found 299.168; 299 (M⁺, 39.7), 132 (65.6), 104 (58.4), 91 (100).
3b: ¹H NMR (200 MHz, CDCl₃) δ 6.71 (s, 1H, CHPh), 6.77-6.85 (m, 2H), 7.05-7.38 (m, 16H), 7.56-7.62 (m, 2H); IR (CDCl₃) 3061 (w), 3064 (w), 3028 (w), 1590, 1492 (s), 1448 (w), 1360, 1310, 1292, 1255 (w), 1231 (w), 1179 (w), 1077 (w), 1029 (w) cm⁻¹; MS (EI) *m/e* calc'd for C₂₆H₂₁N: 347.192, found 347.180; 347 (M⁺, 46.1), 180 (100), 77 (29.7); Analysis calc'd for C₂₆H₂₁N: C, 89.89; H, 6.09; N, 4.03; found: C, 90.05; H, 6.43; N, 3.96.
3c: ¹H NMR (200 MHz, CDCl₃) δ 6.85-7.09 (m, 8H), 7.20-7.30 (m, 8H), 7.35 (s, 1H, CHPh), 8.12-8.15 (m, 2H); IR (CDCl₃) 3083 (w), 3064 (w), 3028 (w), 1624 (w), 1598, 1493, 1479, 1450 (s), 1384, 1335, 1314, 1232, 1151 (w), 1028 (w) cm⁻¹; MS (EI) *m/e* calc'd for C₂₆H₁₉N: 345.1517, found 345.1513; 345 (M⁺, 100), 267 (25.8), 178 (47.5), 167 (carbazole⁺, 63.6).
- This is deduced from the experimental data that 9-*H*-carbazole and diphenylamine have pKs in DMSO of 19.9^{4a} and 24.95 (Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *J. Org. Chem.* **1980**, *45*, 3305) respectively.
- DMF was dried by destroying metallic Na (2 g) in DMF (500 mL)⁷ and then distilling at reduced pressure.
- 5**: mp 55-56°C (55-56°C, Inaba, S.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373; 56°C, Fischer, A.; Grigor, B. A.; Packer, J.; Vaughan, J. *J. Am. Chem. Soc.* **1961**, *83*, 4208).
- Filimonov, V. D.; Rodionov, V. A.; Negrash, V. B. *Khim. Khim. Tekhnol. Geol., Mater. Reg. Nauchno-Prakt. Konf. "Molodye Uch. Spets. Nar. Khoz."*, 3rd **1980**, 75; *Chem. Abstr.* **1982**, *97*, 161993u.
- The mineral acid is a required reagent for the hydrolysis. Attempts to hydrolyze enamine **3c** in acetic acid/water (18:2 mL) failed.

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