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A new and convenient one-pot solid supported synthesis of 2,4,6-triarylpyridines

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Abstract—A new, convenient, efficient and cost-effective one-pot solid supported synthesis of 2,4,6-triarylpyridines from benzylideneacetophenones and urea, thiourea or their derivatives, using Bi(III) nitrate–Al_2O_3 is described. The reaction seems to proceed via β-oxygenation of Bi(III)-enolized benzylideneacetophenone followed by Michael addition, heteroannulation with simultaneous *retro aldol* disproportionation and subsequent catalytic oxidation and dehydration.

2,4,6-Triarylpyridines are structurally related to symmetrical triaryl-thiopyrylium, -selenopyrylium and -telluropyrylium photosensitizers, which have been recommended for photodynamic cell-specific cancer therapy.[1] The compounds are highly stable yet sterically hindered bases and are capable of undergoing facile elimination, as pyridinium ions,[2] during a chemical reaction. Such bases serve as useful substrates in the preparation of stereoselective reagents[3] for the transformation of organic compounds. 2,4,6-Triarylpyridinium derivatives have been used in bringing about nucleophilic displacement,[4] C-alkylation of β-diketones[5] via a chain radical mechanism, electrophilic amination[6] and synthesis of azepines.[7]

Most of the known syntheses[8] of 2,4,6-triarylpyridines are multistage, low to moderately yielding laborious processes and involve harsh or environmentally hazardous reaction conditions. A few syntheses have been accomplished employing heterocyclic compounds,[7,9] sometimes complex ones,[10] while other syntheses[10,11] involve the use of triarylpyridinium substrates. We therefore felt that there was a need to develop an improved straightforward solid supported method for the synthesis of 2,4,6-triarylpyridines. Herein, we report a simple, efficient and cost-effective one-pot solid-supported synthetic method for the synthesis of these compounds from benzylideneacetophenones and urea, thiourea or their derivatives, using the hitherto unexplored Bi(III) nitrate–Al_2O_3 catalyst.

Although Bi(III) nitrate is easily available in pure form and has low toxicity[12] and high stability in air and moisture, its catalytic efficacy has not been thoroughly explored. This led us to evaluate the possible catalytic potential of Bi(III) nitrate immobilized on neutral alumina for the synthesis of nitrogen heterocycles. The catalyst was chosen on the assumption that Bi(III) ions, being on the borderline of hard and soft acids,[13] could bind efficiently to the surface of neutral alumina, prevent its restructuring,[14] synergize its catalytic activity[15,17c] and initiate a reaction under mild conditions. The catalyst was prepared by adsorbing Bi(III) nitrate (5% w/w) on neutral alumina and activation of the air-dried mixture in a hot air oven, at 110 ± 5 °C for 6 h. The catalyst was reactivated, each time, before use.

The substrate benzylideneacetophenones **1a**–**k** were prepared from the appropriate benzaldehyde and acetophenone by the well known Claisen–Schmidt condensation.[16] Subsequent reactions of **1a**–**k** with urea **2a**, (2:1 M) and a stoichiometric amount of Bi(III) nitrate–Al_2O_3, were carried out in a thermostatically controlled hot air oven, at 130 ± 5 °C, for 3–3.5 h. The resulting products **3a**–**k** (65–80% yield) were isolated with chloroform, purified by column chromatography and analyzed by spectral methods, HREIMS, IR, ^{1}H NMR and

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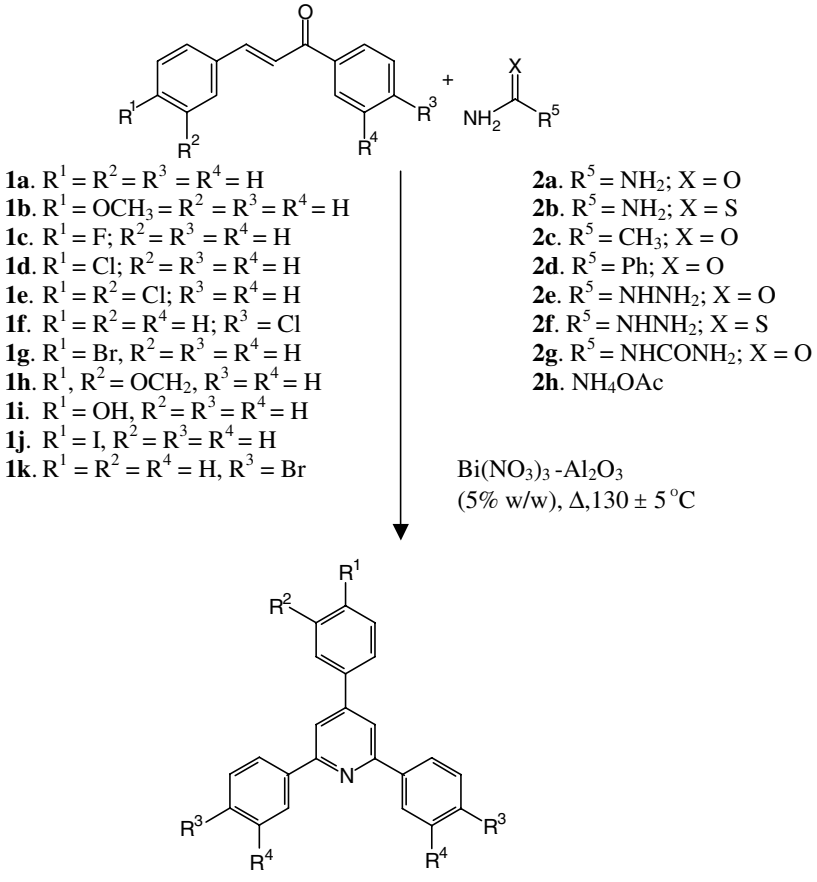
^{13}C NMR. The spectra established the structures of **3a–k** as 2,4,6-triarylpyridine derivatives (Scheme 1). The expanded peak segregated ^{1}H NMR spectra of the products showed characteristic two proton singlets near δ 7.20, due to the protons of the pyridine nucleus.[8c] ^{13}C NMR signals were assigned on the basis of DEPT 135 experiments. The mass fragmentation of the compounds was characteristic of pyridines with a molecular ion peak as the base peak, except for compound **3a** whose MS showed the base peak at *m/z* 77 ($C_6H_5^+$). Except for compounds **3f** and **3k**, which possessed two monosubstituted phenyl rings at positions 2 and 6 of the pyridine nucleus, and compound **3a**, which possessed unsubstituted phenyl rings at positions 2, 4 and 6 of the nucleus, all products had a lone substituted phenyl ring at position 4 of the pyridine nucleus.

X-ray crystallography of **3b** (Fig. 1), as a representative product, confirmed the structure and proved the presence of only one 4-methoxyphenyl ring at position 4 of the pyridine nucleus.

To generalize this reaction, benzylideneacetophenones **1a–d** were reacted, separately but under identical conditions, with thiourea **2b**, acetamide **2c**, benzamide **2d**, and biuret **2g**, using Bi(III) nitrate–Al_2O_3. These reactions afforded products **3a–d** in percentage yields comparable to the yields obtained by the reaction of benzylideneacetophenones **1a–d** with urea. One of the minor constituents in the product mixture obtained from the reaction of **1a–d** with benzamide was identified as benzoic acid. In addition to product **3**, all reactions afforded minor quantities of the original aldehyde from which compounds **1a–k** were prepared. On repeating, the reactions of **1a–d** with semicarbazide **2e**, and thiosemicarbazide **2f**, 2,4,6-triarylpyridines were recovered in moderate yields (50–68%) (Table 1). The reactions of **1a–d** with **2e** also yielded minor quantities of 5,7-diaryl-1,2,4-triazepin-2,4-dien-3-ols **4a–d** (Scheme 3), in addition to **3a–d** and the original aldehydes.

Since alumina chemisorbs water readily[17] and retains it even after activation at 110 ± 5 °C, the mechanism of the reaction may be rationalized as involving β-oxygenation of the Bi(III) activated benzylideneacetophenone enolate, which may then undergo a Michael addition to a second α,β-unsaturated ketone (Scheme 3) to form a 1,5-diketone enolate adduct. Subsequent heteroannulation with urea or its derivatives via condensation and *retro aldol* disproportionation[18] may lead to the formation of 2-hydroxy-2,4,6-triaryltetrahydropyridine derivatives, which on dehydration and oxidation may yield



Scheme 1. Triarylpyridines from benzylideneacetophenones.

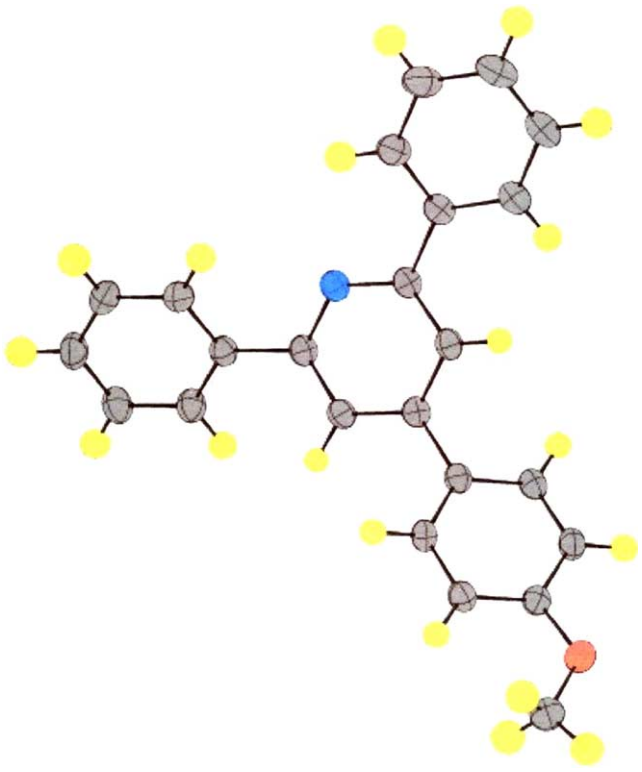


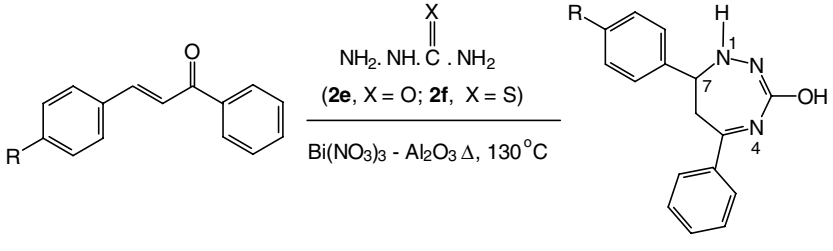
Figure 1. ORTEP representation of compound **3b**.

2,4,6-triarylpyridines after hydrolysis. This mechanism is supported by the fact that the products obtained from 4-substituted benzylideneacetophenones, like **3b**, possessed only one substituted phenyl group, at position 4 of the pyridine nucleus. To substantiate the proposed mechanism, cross-reactions of benzylideneacetophenones with equimolar amounts of urea and stoichiometric quantities of Bi(III) nitrate–Al_2O_3 were carried out at 130 ± 5 °C (Scheme 4). The reaction of **1b**, **1f** and **2a** yielded **3b** (30%), **3f** (28%) and **3l** (35%), and the reaction involving **1b**, **2a** and *p*-chloroacetophenone (1:1:1) gave **3b** and **3l**, in nearly equal proportions.

We attempted the reaction of equimolar quantities of **1b**, *p*-chloroacetophenone and a stoichiometric amount of the Bi(III) nitrate–Al_2O_3 in the absence of urea or its derivatives, at 130 ± 5 °C (Scheme 5). The reaction afforded two products, **5a** and **5b**, which were separated by column chromatography and identified, by spectral methods, as 2-(4-methoxyphenyl)-hydroxymethyl-3-(4-methoxy)phenyl-1,5-diphenylpentan-4-en-5-ol-1-one **5a** and 1-(4-chloro phenyl)-3-(4-methoxy)phenyl-5-phenylpentan-4-en-5-ol-1-one **5b** (Scheme 5). The ^{1}H NMR, ^{13}C NMR and DEPT 135 spectra of **5a** and **5b** showed the presence of a carbonyl group, δ_C 197.3, and an enol hydroxyl, δ 12.9 (s br, exch. D_2O, 1H). The spectra of **5a** revealed the absence of a methylene carbon whose presence in **5b** was evident from the

Table 1. Percent yield of products **3a**–**k** using different amino derivatives (**2a**–**d**) and enones (**1a**–**k**)

Product	% Yield with different amino compounds									
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**MW**	Time (MW) (min)
3a	80	78	82	78	50	65	79	32	78	15
3b	79	80	80	70	52	60	80	34	80	10
3c	78	71	76	62	68	55	76	30	78	12
3d	72	72	68	60	66	60	74	31	70	12
3e	70	—	—	—	—	—	—	31	—	—
3f	66	—	—	—	—	—	—	28	—	—
3g	69	—	—	—	—	—	—	25	—	—
3h	76	—	—	—	—	—	—	32	—	—
3i	65	—	—	—	—	—	—	29	—	—
3j	73	—	—	—	—	—	—	41	—	—
3k	72	70	60	—	—	—	—	38	—	—



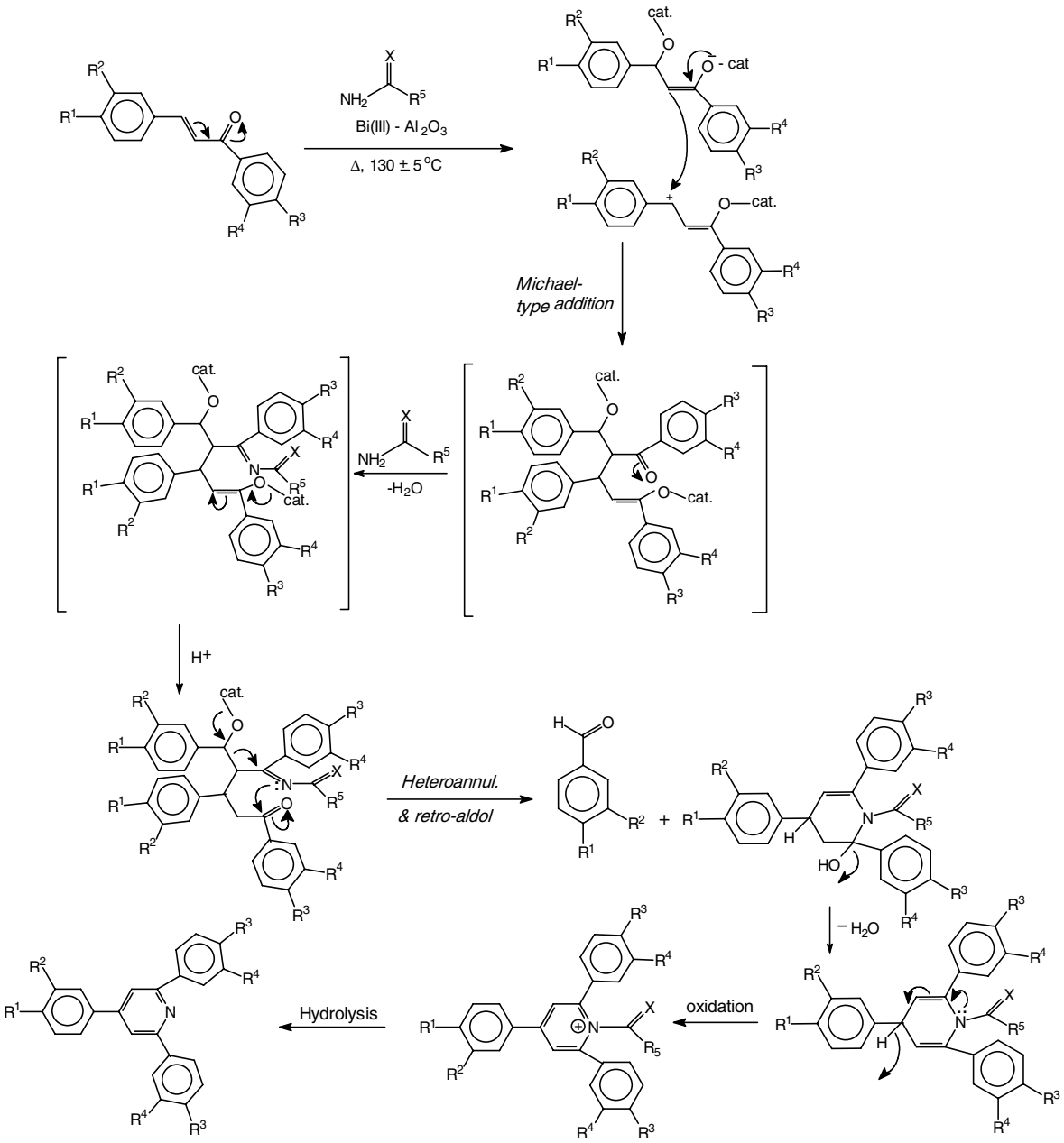
4a; R = H (26%)

4b; R = OCH_3 (20%)

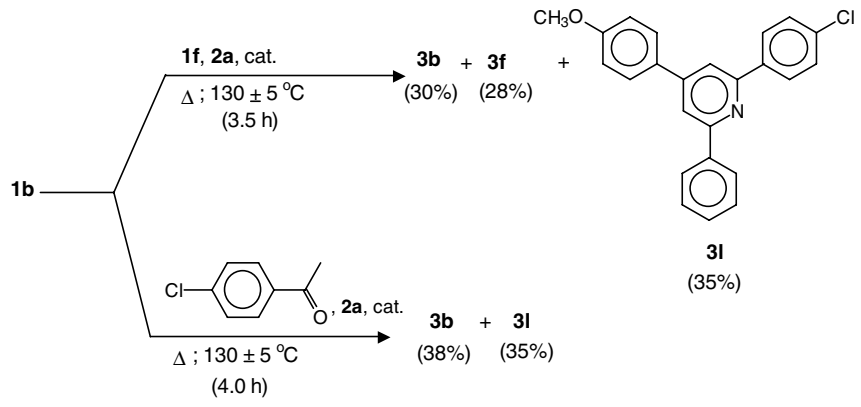
4c; R = F (16%)

4d; R = Cl (18%)

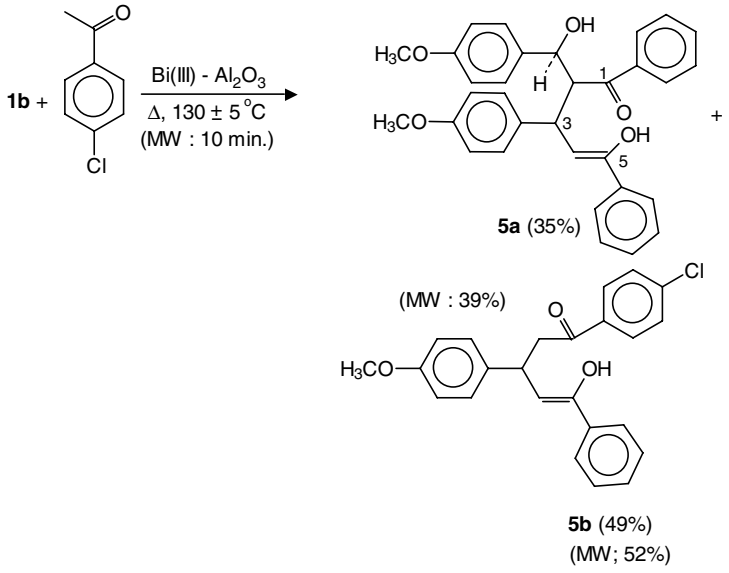
Scheme 2. 5,7-Diaryl-1,2,4-triazepin-3-ol from benzylideneacetophenone.



Scheme 3. Possible mechanism for the formation of 2,4,6-triarylpyridines.



Scheme 4. Cross-reactions of **1b**.



Scheme 5. Reaction of **1b** and *p*-chloroacetophenone in the absence of urea.

resonance signals at δ 2.69 (d, $J = 4.5$ Hz, 2H), in its ^{1}H NMR spectrum, and δ_C 25.3, in its ^{13}C NMR and DEPT 135 spectra. The spectra of **5a** showed the presence of a secondary hydroxyl displaying resonance signals at δ 2.80 (s br, exch. D_2O, 1H) and 5.01 (d, $J = 3.6$ Hz, 1H; –C*H*OH), δ_C 83.2. These signals were absent in the spectra of **5b**. These observations were consistent with the proposed mechanism and indicated that the *retro-aldol* disproportionation is probably triggered by heteroannulation of the Michael adduct with urea or its derivatives.

As most of the earlier syntheses[8] of 2,4,6-triarylpyridines employed ammonium acetate **2h**, as the source of ammonia, we felt it obligatory to make use of it in the present reaction. 2,4,6-Triarylpyridines were obtained, albeit in poor yields (Table 1), under our reaction conditions. The minor products **4a**–**d**, in the reaction of **1a**–**d** and **2e** (Scheme 2) may result from a direct Michael addition to the Bi(III)-enolized benzylideneacetophenone followed by cyclodehydration. The reaction is sensitive to temperature; the optimum temperature being 130 ± 5 °C. The reaction failed to proceed in solution and also on using neat Al_2O_3 or Bi(III) nitrate as the reagent. We repeated the reactions of **1a**–**d**, **2a** and Bi(III)–Al_2O_3 (Scheme 1) and also the reaction of **1b**, *p*-chloroacetophenone and Bi(III)–Al_2O_3 (Scheme 5) in a domestic microwave (2450 MHz), at 60% power using the procedure of Mukhopadhyay et al.,[19] which allows the temperature to remain at ca. 130 °C. The reactions were complete in 10–15 min without any appreciable improvement in the yields of the 2,4,6-triarylpyridines.

In summary, we have devised a new, one-pot, and general solid supported catalytic method for the synthesis of 2,4,6-triarylpyridines from benzylideneacetophenone and urea, thiourea or their derivatives using $Bi(NO_3)_3$ immobilized on Al_2O_3 as the reagent. An advantage of this method is the low toxicity of bismuth.[12] Further studies of the scope and limitations of immobilized Bi(III) nitrate in organic transformations are under investigation.

A representative procedure for the preparation of the Bi(III) nitrate–Al_2O_3 and the synthesis of 2,4,6-triarylpyridines and the spectral data (IR, ^{1}H NMR, ^{13}C NMR, HREIMS) are available as a supplement to this letter. X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre CCDC 198750.

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