REACTION OF *N*-BENZYLIDENEANILINES WITH METHYL 3-AMINOCROTONATE CATALYZED BY INORGANIC SOLIDS

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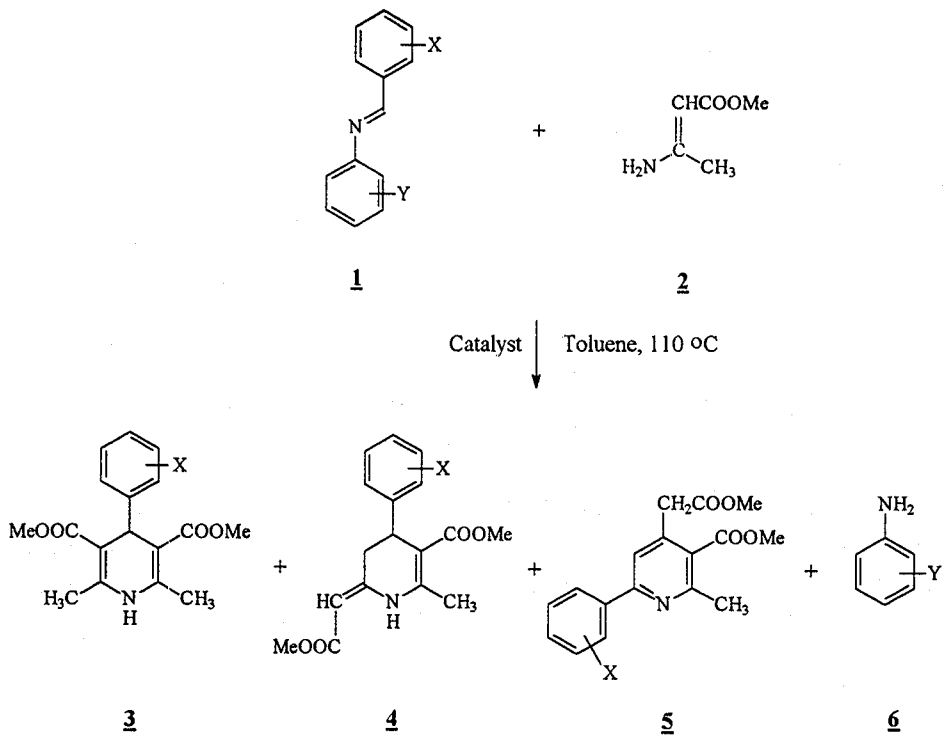
Abstract: *N*-benzylideneanilines **1** react with methyl 3-aminocrotonate **2** in the presence of solid acidic catalysts (K10 montmorillonite or ZF520 zeolite) to give dimethyl 4-(substituted)phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates **3** as major products. Methyl 2-(methoxycarbonylmethylene)-6-methyl-4-(substituted)phenyl-1,2,3,4-tetrahydro-5-pyridinecarboxylates **4** and methyl 4-(methoxycarbonylmethyl)-2-methyl-6-(substituted)phenyl-3-pyridinecarboxylates **5** were isolated as minor products.

Introduction

A series of carbon-carbon bond formation processes, such as cycloaddition reactions of the Diels-Alder type and condensation reactions can be promoted by clay catalysts or clay-supported reagents (1,2). In 1994 we reported a novel K10 montmorillonite catalyzed 1,4-dihydropyridine synthesis starting from aromatic aldehyde azines (3). As a contribution to the study of other Schiff bases we have focussed our attention on imines derived from anilines and aryl aldehydes.

Unique reactivities of imines which serve as both azadienes and dienophiles under certain conditions have been revealed (4-6). *N*-benzylideneanilines have been shown to participate as 2-aza-1,3-diene systems (4-14) in a range of [4+2] cycloadditions with electron-rich olefins in the presence of protic or Lewis acid catalysts to give (tetrahydro)quinoline derivatives. Carboxylic acids (8,9), boron trifluoride etherate (4-8,12), iron(III) chloride (8,10,11), iron(III)-doped montmorillonite (K10/Fe^{3+}) (10) and lanthanide triflates (13,14) are employed to promote these reactions. Electron-rich dienes react with *N*-phenylbenzylimines under the influence of Lewis acids, such as zinc chloride (15) and ytterbium triflate (13) to afford tetrahydropyridine derivatives. Addition of enamines (16) or trimethylsilyl ketene acetals (14,17,18) to imines affords β-aminoesters. The reaction can be accomplished at high pressure (16), in the presence of ytterbium(III) triflate (14), Fe^{3+}-montmorillonite (17), or K10 montmorillonite under microwave irradiation (18).



Scheme 1

Table 1. Reaction of *N*-benzylideneanilines **1** with methyl 3-aminocrotonate **2**

Entry	1	X	Y	Catalyst	3	Yield %	4	Yield %	5	Yield %	Σ3+4+5 %
1	1a	H	H	-	3a	-					
2	1a	H	H	SiO_2	3a	43					
3	1a	H	H	K10	3a	52	4a	10	5a	6	68
4	1a	H	H	ZF520	3a	40	4a	18	5a	11	69
5	1b	H	3-NO_2	K10	3a	52	4a	9	5a	7	68
6	1b	H	3-NO_2	ZF520	3a	33	4a	19	5a	10	62
7	1c	3-NO_2	H	SiO_2	3b	56					
8	1c	3-NO_2	H	K10	3b	72	4b	5	5b	2	79
9	1c	3-NO_2	H	ZF520	3b	68	4b	9	5b	7	84
10	1d	3-NO_2	3-NO_2	K10	3b	71	4b	4			
11	1e	2-NO_2	3-NO_2	K10	3c	65					
12	1f	2,3-Cl_2	3-NO_2	K10	3d	57	4d	4	5d		
13	1g	3,4-$(MeO)_2$	H	K10	3e	38	4e	19	5e	16	73

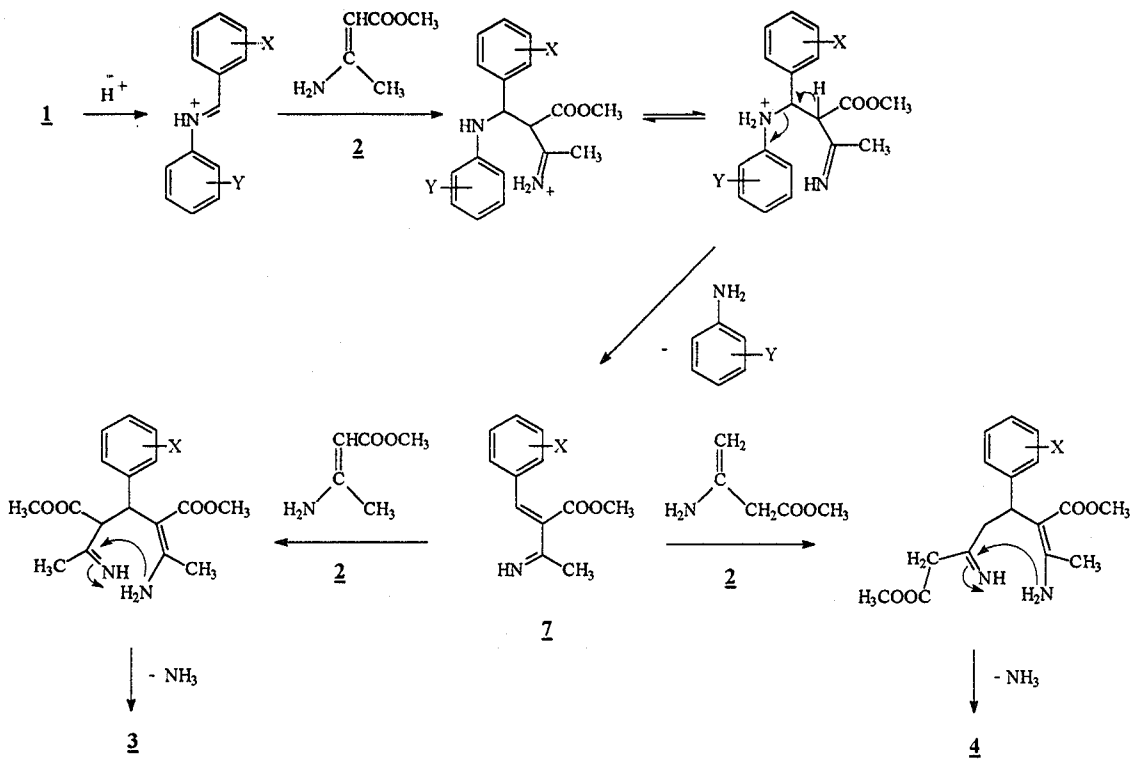
No reaction was observed in the absence of a catalyst.
Yields of isolated products are given.
The elemental analyses for C, H, N , Cl were within ± 0.4 % of the theoretical values.
5d could not be separated from m-nitroaniline **6** by column chromatography.

Results and Discussion

We have found that both *N*-benzylideneanilines **1** and benzaldehyde azines (3) behaved in a similar fashion when treated with methyl 3-aminocrotonate **2**. The presence of an acidic catalyst is essential to the success of the reaction. Catalysts tested include K10 montmorillonite, ZF520 zeolite and silica gel. Dimethyl 4-(substituted)phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates **3a-e** were obtained in 33-72 % yields depending on the catalyst used and the nature of the substituents on the benzylidene moiety [X = H, 2-NO_2 , 3-NO_2 , 2,3-Cl_2 , 3,4-$(MeO)_2$]. Besides compounds **3** methyl 2-(methoxycarbonylmethylene)-6-methyl-4-(substituted)phenyl-1,2,3,4-tetrahydro-5-pyridine-carboxylates **4a,b,d,e** (3) and methyl 4-(methoxycarbonylmethyl)-2-methyl-6-(substituted)phenyl-3-pyridinecarboxylates **5a,b,e** (3) were isolated as minor products. (Scheme1, Table 1) Such by-products are quite unusual in 1,4-dihydropyridine syntheses (19). There are only few reports of 2-alkylidene-1,2,3,4-tetrahydropyridine derivatives (20-22).

Higher yields and selectivities of 1,4-dihydropyridines were obtained by K10 montmorillonite (**3a** : **4a** = 5.2 , entry 3 and **3a** : **4a** = 5.8 , entry 5), while higher yields of tetrahydropyridines were afforded by ZF520 zeolite (**3a** : **4a** = 2.22 , entry 4 and **3a** : **4a** = 1.74 , entry 6). The product distribution and yields are not influenced by the presence of an electron-withdrawing substituent in the aniline ring (Y = 3-NO_2) (See entries 3 and 5 or entries 4 and 6 or entries 8 and 10). On the other hand formation of 1,4-dihydropyridine **3b** having an electron-withdrawing substituent (X = 3-NO_2) is favored. Formation of 1,4-dihydropyridine **3e** having electron donor substituents [X = 3,4-$(MeO)_2$] is unfavorable.

Compounds with acidic CH hydrogens add to *N*-benzylideneanilines **1** (23). The presence of an electron-withdrawing substituent in the phenylmethylene ring increases the electrophile character of the masked aldehyde carbon and facilitates its attack by the enamine **2**. Addition of the unfavorable tautomeric form $CH_2=C(NH_2)CH_2COOCH_3$ of **2** leads to the formation of tetrahydropyridine **4** in lower yields (Scheme 2)



Scheme 2

Conclusion

In summary, reaction of *N*-benzylideneanilines **1** with methyl 3-aminocrotonate **2** under heterogeneous conditions provides a new approach to symmetrically substituted 1,4-dihydropyridines **3**, multifunctionalized tetrahydropyridines **4** and pyridines **5**. Product selectivity can be modified by the catalyst and by the substituent on the phenylmethylene group.

Experimental

All melting points are uncorrected. The ^{1}H-NMR spectra were recorded in $CDCl_3$ with Bruker AC-400 spectrometer. Chemical Shifts were determined on the δ scale using tetramethylsilane (δ = 0) as internal standard. Mass spectra were measured with an MS-902 spectrometer operating at 70 eV. Silica gel 60 (Merck, 70-230 mesh ASTM) was used for column chromatography. *N*-benzylideneanilines **1a-g** were prepared according to known procedure (24).

Catalysts used were: K10 montmorillonite (Süd-Chemie, Munich)

ZF520 zeolite (Zéocat, Paris)

Silica gel 60 (Merck, 70-230 mesh ASTM)

Reaction of *N*-benzylideneanilines 1a-g with methyl 3-aminocrotonate 2 - General procedure

A mixture of *N*-benzylideneaniline **1a-g** (0.01 mol), methyl 3-aminocrotonate **2** (2.30 g, 0.02 mol), catalyst (4 g), and toluene (50 ml) was stirred at 110 °C for 8 h. The catalyst was filtered off from the hot reaction mixture and washed with $CHCl_3$ (50 ml). 1,4-Dihydropyridines (**3a**, 40-43 %; **3b**, 55-65 %) were filtered off from toluene after cooling. The combined filtrate (toluene and $CHCl_3$) was evaporated and the residue was subjected to column chromatography using *n*-hexane/ethyl acetate (100 : 1 -1 : 1) solvent mixture as eluent to give tetrahydropyridines **4a,b**, 2-arylpyridines **5a,b**, and an additional 5-12 % of 1,4-dihydropyridines **3a,b**.

Column chromatography (*n*-hexane/ethyl acetate 100 : 1 -1 : 1) was applied for the preparation of compounds **6** (Y = 3-NO_2, 74 %) and **3c** (65 %). Preparation of **4d**, **6** (Y = 3-NO_2, 95 %) and **3d** was similarly accomplished. **5d** could not be isolated by this method because it was eluted together with m-nitroaniline. Compounds **4e**, **5e** and **3e** were obtained by column chromatography using the same eluent as above.

Yields are summarized in Table 1.

3a	m.p. 197-198 °C (EtOH)	Lit. (25) m.p. 197-198 °C (MeOH)	MS m/z: 301 (M^+)
3b	m.p. 208 °C (MeOH)	Lit. (25) m.p. 209-210 °C (MeOH)	MS m/z: 346 (M^+)
3c	m.p. 175-176 °C (MeOH)	Lit. (26) m.p. 171 °C (EtOH-H_2O)	MS m/z: 346 (M^+)
3d	m.p. 188-189 °C (MeOH)	Lit. (27) m.p. 185-187 °C (MeOH)	MS m/z: 369 (M^+)
3e	m.p. 147-148 °C (MeOH)	Lit. (28) m.p. 145-146 °C	MS m/z: 361 (M^+)
4a	m.p. 128-129 °C (MeOH)	Lit. (3) m.p. 127-128 °C (MeOH)	MS m/z: 301 (M^+)
4b	m.p. 163-164 °C (MeOH)	Lit. (3) m.p. 163 °C (MeOH)	MS m/z: 346 (M^+)
4d	m.p. 153-154 °C (MeOH)	Lit. (3) m.p. 151-152 °C (MeOH)	MS m/z: 369 (M^+)
4e	m.p. 136-137 °C (EtOAc)	Lit. (3) m.p. 135 °C (MeOH)	MS m/z: 361 (M^+)
5a	m.p. 72-73 °C	Lit. (3) m.p. 72-73 °C	MS m/z: 299 (M^+)
5b	m.p. 132-133 °C (*i*-Pr_2O)	Lit. (3) m.p. 132-134 °C (*i*-Pr_2O)	MS m/z: 344 (M^+)
5e	m.p. 100-101 °C (*i*-Pr_2O)	Lit. (3) m.p. 101-102 °C (*i*-Pr_2O)	MS m/z: 359 (M^+)

For the ^{1}H-NMR data of tetrahydropyridines **4a-e** and 2-arylpyridines **5a,b,e** see Tables 2 and 3.

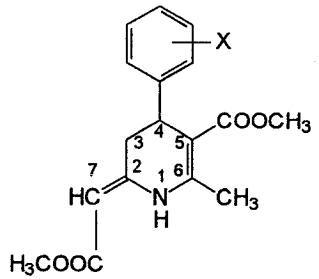


Table 2. ^{1}H NMR Data of Compounds **4**

No.	X	1-H	7-H	3-H_A	3-H_B	4-H	4-aryl	5-$COOCH_3$ 7-$COOCH_3$	6-CH_3
4a	H	9.94 br	4.66d (*J*=2 Hz)	2.48 dd (*J*=15 Hz) (*J*=2 Hz)	2.94 ddd (*J*=15 Hz) (*J*=7 Hz) (*J*=2 Hz)	4.11 dd (*J*=7 Hz) (*J*=2 Hz)	7.10-7.27 m	3.61 s 3.65 s	2.48 s
4b	3-NO_2	10.01 br	4.70 d (*J*=1.9 Hz)	2.50 dd (*J*=15 Hz) (*J*=2 Hz)	3.01 ddd (*J*=15 Hz) (*J*=7 Hz) (*J*=1.9 Hz)	4.23 dd (*J*=7 Hz) (*J*=2 Hz)	7.42-7.44m (2H) 8.00-8.01m (1H) 8.03-8.08m (1H)	3.63 s 3.67 s	2.52 s
4d	2,3-Cl_2	9.94 br	4.62 d (*J*=1.5 Hz)	2.52 dd (*J*=16 Hz) (*J*=2 Hz)	2.91 ddd (*J*=16 Hz) (*J*=7 Hz) (*J*=2 Hz)	4.63 d, br (*J*=7 Hz)	6.84 dd (1H, *J*=8 Hz, *J*=2 Hz) 7.07 dd (1H, *J*=8 Hz, *J*=8 Hz) 7.31 dd (1H, *J*=8 Hz, *J*=2 Hz)	3.59 s 3.65 s	2.54s
4e	3,4-$(MeO)_2$	9.93 br	4.69 d (*J*=1.7 Hz)	2.47 dd (*J*=15.5 Hz) (*J*=2 Hz)	2.91 ddd (*J*=15.5 Hz) (*J*=6.9 Hz) (*J*=1.7 Hz)	4.06 d, br (*J*=6.9 Hz)	3.82 s, 3.83 s 2xOCH_3 6.74 d (1H, *J*=8.2 Hz) 6.68 d (1H, *J*=2.1 Hz) 6.65 ddd (1H, *J*=8.2, *J*=2.1, *J*=0.8 Hz)	3.64 s 3.66 s	2.47s

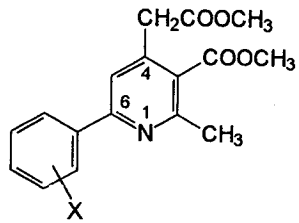


Table 3. ^{1}H NMR Data of Compounds **5**

No.	X	5-H	4-CH_2COOCH_3	6-aryl	3-$COOCH_3$ 4-CH_2COOCH_3	2-CH_3
5a	H	7.40-7.50 m	3.81 s	7.40-7.50 m (4H) 7.98-8.02 m (2H)	3.71 s 3.93 s	2.71 s
5b	3-NO_2	7.59 s	3.86 s	7.68 dd (1H, *J*=8 Hz) 8.30 ddd (1H, *J*=8 Hz, *J*=2 Hz, *J*=1 Hz) 8.42 ddd (1H, *J*=8 Hz, *J*=2 Hz, *J*=1 Hz) 8.87 dd (1H, *J*=2 Hz, *J*=2 Hz)	3.74 s 3.96 s	2.76 s
5e	3,4-$(MeO)_2$	7.42 s	3.82 s	3.92 s, 3.94 s 2xOCH_3 6.95 d (1H, *J*=8.2 Hz) 7.55 dd (1H, *J*=8.2 Hz, *J*=2 Hz) 7.66 d (1H, *J*=2 Hz)	3.71 s 4.00 s	2.70 s

References

1. P. Laszlo (Ed.), Preparative Chemistry Using Supported Reagents, Academic Press, San Diego, 1987
2. M. Balogh and P. Laszlo, Organic Chemistry Using Clays, Springer Verlag, Berlin, 1993
3. M. Balogh, E. Gács-Baitz, K. Simon and I. Hermecz, ACH - Models in Chemistry, 131, 383 (1994)
4. T. Wagner-Jauregg, Synthesis, 349 (1976)
5. D.L. Boger, Tetrahedron, 39, 2869 (1983)
6. D.L. Boger and S.M. Weinreb, Hetero Diels-Alder Methodology in Organic Synthesis, Academic Press, San Diego, 1987 (Chapters 2.5 and 9.2)
7. T. Kametani, H. Takeda, Y. Suzuki and T. Honda, Synth. Commun. 15, 499 (1985)
8. T.L. Gilchrist and A.M. Stannard, Tetrahedron Lett. 29, 3585 (1988)
9. P.A. Grieco and A. Bahsas, Tetrahedron Lett. 29, 5855 (1988)
10. J. Cabral and P. Laszlo, Tetrahedron Lett. 30, 7237 (1989)
11. R. Leardini, D. Nanni, A. Tundo, G. Zanardi and F. Ruggieri, J. Org. Chem. 57, 1842 (1992)
12. K. Narasaka and T. Shibata, Heterocycles, 35, 1039 (1993)
13. S. Kobayashi, H. Ishitani and S. Nagayama, Synthesis, 1195 (1995)
14. Y. Makioka, T. Shindo, Y. Taniguchi, K. Takaki and Y. Fujiwara, Synthesis, 801 (1995)
15. J. Barluenga, F. Aznar, C. Valdes and M.P. Cabal, J. Org. Chem. 58, 3391 (1993)
16. R.W.M. Aben, R. Smit and J.W. Scheeren, J. Org. Chem. 52, 365 (1987)
17. M. Onaka, R. Ohno, N. Yanagiya and Y. Izumi, Synlett, 141 (1993)
18. F. Texier-Boullet, R. Latouche and J. Hamelin, Tetrahedron Lett. 34, 2123 (1993)
19. D.M. Stout and A.I. Meyers, Chem. Rev. 82, 223 (1982)
20. M.D. Taylor, E.W. Badger, R.P. Steffen, S.J. Haleen, T.A. Pugsley, Y.H. Shih and R.E. Weishaar, J. Med. Chem. 31, 1659 (1988)
21. J.W. Patterson and J.T. Nelson, J. Heterocyclic Chem. 25, 125 (1988)
22. C.N. O'Callaghan, T.B.H. McMurry, H. Meyer and W. Seidel, Chem. Ind. (London), 833 (1990)
23. R.W. Layer, Chem. Rev. 63, 489 ((1963)
24. L.A. Bigelow and H. Eatough, Organic Syntheses, Collect. Vol. 1, 80 (1947) Wiley, New York
25. A.P. Phillips, J. Am. Chem. Soc. 71, 4003 (1949)
26. K. Görlitzer and D. Buß, Arch. Pharm.(Weinheim), 314, 938 (1981)
27. R.A. Coburn, M.Wierzba, M.J. Suto, A.J. Solo, A.M. Triggle and D.J. Triggle, J. Med. Chem. 31, 2103 (1988)
28. H. Iwamoto, M. Satoh, N. Nagano, T. Koide and H. Ikadai, Eur. Patent Appl. 285,267 (1988), Chem. Abstr. 110, 154156g (1989).

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