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DIASTEREO SELECTIVITY IN ASYMMETRIC MICHAEL ADDITION OF A-METHYLBENZYLAMINES TO A, B-UNSATURATED CARBONYL COMPOUNDS

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ABSTRACT

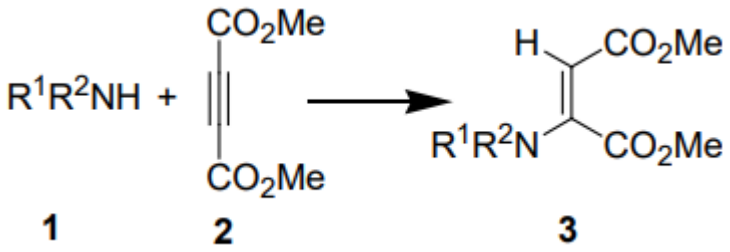
Primary amines are known to produce a combination of cis- and trans-addition products when reacting with dimethyl acetylene dicarboxylate (DMAD) and methyl propiolate, however secondary amines are claimed to produce solely the trans-product. In addition, it was discovered that the trans-addition product forms under kinetic control. On the other hand, the trans-product largely converted to the thermodynamically more stable cis-product after being left in solution at room temperature for some time or upon heating. Products are obtained by the reaction of amines (6a-h) with methyl propiolate (7) in methylene chloride at room temperature (25oC) (8). Mixed compounds (8e and 8e') were obtained from the reaction with benzylamine (6e). C=O groups are present when there is a distinct absorption band between 1605 and 1696 cm-1. As a consequence of the C=C stretching vibration, an absorption band may be seen between 1508 and 1604 cm-1. There is a strong band between 1100 and 1251 cm1 that has been attributed to C-O stretching vibration. All reactions were performed in oven-dried glassware using inert anhydrous solvents in a nitrogen atmosphere. All chemicals and reagents were of commercial quality, acquired from Sigma-Aldrich, and used as is. This stereoselective addition of secondary amines to methyl propiolate results in the formation of trans-methyl -(dialkylamino) acrylate.

KEYWORDSMETHY**,**chromatography, Atmosphere, Reagents, Mixed, Compunds

INTRODUCTION

In this extensive overview of aza-Michael addition, its use in the synthesis of several bioactive and other valuable precursors was emphasized. The cis-trans stereoselectivity and the mechanism of the cis-trans isomerization of the reaction between amines and acetylene carboxylic acid esters have garnered a great deal of interest in this context. Reactions between primary amines and DMAD or methyl propiolate have been reported to produce a combination of cis- and trans-addition products, whereas reactions between secondary amines and DMAD or methyl propiolate produce solely the trans-product. It was also discovered that the trans-addition product formed under kinetic control. After being left in solution at room temperature or heated, however, the trans-product primarily converted into the thermodynamically more stable cis-product. The latter was found to be more stable because of the intramolecular hydrogen bonding between the N-H proton and the C=O moiety of the ester group.

Despite the fact that certain reasonable processes have been presented for transforming the trans-product into the cis-isomer, it may be impossible to isolate the required intermediate. Isolation of the intermediate molecule 5 resulting from an intramolecular 1,4.-prototropic shift in the first generated addition product 4 of benzylamine was recently reported by our research group in a study of the Michael addition of primary and secondary amines with DMAD (Scheme 1). (Figure 1). An intermediary inMotivated by the above, we set out to conduct a comprehensive study of the Michael addition of benzylamine and secondary amines to methyl propiolate, both experimentally and theoretically. The findings of this paper are organized as follows:



Scheme 1.Michael addition of amines with DMAD.

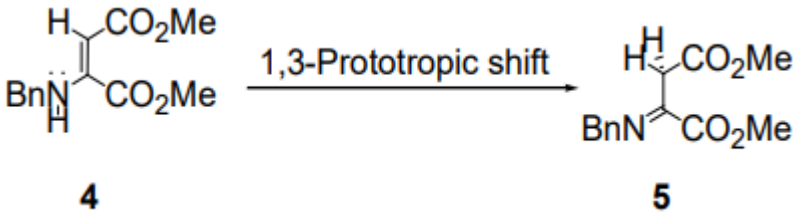


Figure 1. 1,4.-Prototropic shift in the addition product of benzylamine.

LITERATURE REVIEW

Yuan-Yuan Zhu (2021) For building N-acyl phosphinamidites from acyl-phosphine substrates, a novel Staudinger approach involves a distinct C-P bond cleavage rather than N-P bond cleavage. Stereogenic centers that are easily epimerized are protected since the reaction is carried out under moderate circumstances without the use of any catalysts or additives. N2 gas was the sole byproduct in the production of a wide variety of new N-acyl phosphinamidites, such as those with a chiral amino acid skeleton and axial chirality, as well as complicated natural product scaffolds. Preliminary screening findings have shown that these N-acyl phosphinamidites may be used as chiral chemical catalysts, making them a promising new class of P-O ligands.

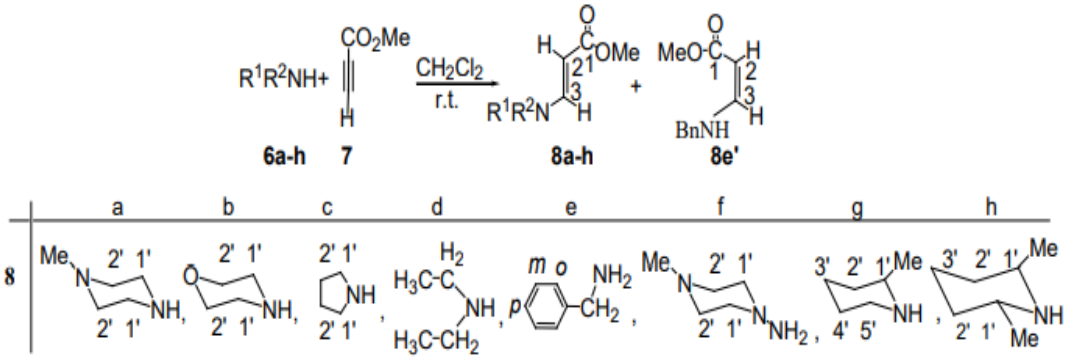
Mehdi Sharifi-Rad (2020)cardiovascular disease, diabetes, neurological disorders, and cancer are just few of the many chronic illnesses in which oxidative stress plays a crucial part in the

etiology. Abnormalities in gene expression may result from exposure to pro-oxidant substances, which can affect the structure of mitochondrial DNA and the activity of several enzymes and cellular structures over time. Oxidative stress is mostly caused by the contemporary lifestyle, which is characterized by processed food, exposure to a broad variety of toxins, and a lack of exercise. Nonetheless, oxidative stress is thought to have a role in various human illnesses, and these diseases have been explored for their potential to be treated or prevented via the use of medicinal plants having antioxidant capabilities. This study focuses on plant-derived antioxidant substances and their mechanisms of antioxidant defenses with an eye on preventing illnesses for which oxidative stress is a risk factor. Lastly, the pros and cons of using antioxidant molecules to lower oxidative stress in a variety of human circumstances are reviewed.

Kour, Manjinder& Gupta, Raakhi&Bansal, Raj. (2017). Experiments and DFT calculations have been performed on the reaction between maleic anhydride and secondary amines such 1-methylpiperazine, pyrrolidine, morpholine, 2-methylpiperidine, and diethylamine. At kinetically controlled temperatures (-78°C or -15°C), amines add across the CO functionality solely, and the addition products generate N-substituted maleimic acid derivatives through isomerization. Even under thermodynamic control, amine does not contribute across the CC functionality in maleic anhydride, in contrast to the acyclic,-unsaturated carbonyl compounds. A closer look of the local condensed Fukui functions reveals that the carbonyl carbon atoms in maleic anhydride are significantly harder than in an acyclic,-unsaturated carbonyl compound like acrolein, providing a plausible explanation for the chemical's behavior. As a result, the amines target the carbonyl group in maleic anhydride rather than any other parts of the molecule.

EXPERIMENTAL RESULTS

Under normal conditions (25 degrees Celsius), the amines (6a-h) react with methyl propiolate (7) in methylene chloride to produce the products (8). Two different compounds, (8e) and (8e'), were obtained by reacting benzylamine (6e). At room temperature (25 °C), the reactions are finished in 4-8 hours and are only mildly exothermic. Except for the benzylamine reaction, which yielded a mixture of two compounds (8e and 8e'), a single product was produced in all other cases. The end results are low-melting-point, crystalline, colorless solids.



Scheme 1.Aza-Michael addition of amines to methyl propiolate.

High yields are achieved, and the products are produced as colorless crystalline solids or viscous mass, soluble in common organic solvents including chloroform, ethyl acetate, and methanol. Element analysis, IR, and H and. C NMR spectrum analyses all provided useful insight into their composition.

CHARACTERIZATION OF THE PRODUCTS

Tables 1 and 2 provide the goods' physical characteristics and spectral characteristics, respectively.

Table1. Physical data of the products obtained from the reaction of amines with methyl propiolate.

Product No.	Physical State	Yield (%)	Melting Point (oC)	Soluble In	Elemental Analysis
8a	Crystalline Solid	88	4.8-40	Ethyl acetate, Chloroform, Methanol	C9H16N2O2 Found: C, 58.4.2; H, 8.60; N, 15.10% Calc.: C, 58.67; H, 8.75; N, 15.21%
8b	Crystalline Solid	91	65-66	Ethyl acetate, Chloroform, Methanol	C8H14.NO4. Found: C, 55.98; H, 7.65; N, 7.96% Calc.: C, 56.14.; H, 7.65; N, 8.18%
8c	Crystalline Solid	79	100-102	Ethyl acetate, Chloroform, Methanol	C8H14.NO2 Found: C, 61.84; H, 8.24.; N, 8.89% Calc.: C, 61.91; H, 8.44; N, 9.04.%

8d	Crystalline Solid	76	57-58	Ethyl acetate, Chloroform, Methanol	C9H16N2O2 Found: C, 61.02; H, 9.40; N, 8.4.6% Calc.: C, 61.12; H, 9.62; N, 8.91%
8e+8e'	Viscous Mass	71	-	Ethyl acetate, Chloroform, Methanol	-
8f	Viscous Mass	80	-	Ethyl acetate, Chloroform, Methanol	C9H17N4.O2 Found: C, 54.90; H, 9.81; N, 7.76%
					Calc.: C, 54.25; H, 9.60; N, 21.09%
8g	Viscous Mass	72	-	Ethyl acetate, Chloroform, Methanol	C10H17NO2 Found: C, 65.62; H, 9.94.; N, 7.76% Calc.: C, 65.54; H, 9.4.5; N, 20.74%
8h	Viscous Mass	70	-	Ethyl acetate, Chloroform, Methanol	C11H19NO2 Found: C, 66.55; H, 9.24.; N, 7.76% Calc.: C, 66.97; H, 9.71; N, 7.10%

Table 2.Spectral data of the products.

Product no.	IR KBr, ν (cm^{-1})	^{1}H NMR δ(ppm), *J*(Hz)	$^{14.}$C NMR δ(ppm), *J*(Hz)
8a	1696 (C=O s), 1520 (C=C s), 1100 (C-O s)	7.4.7 (d, 1H, $^{4.}JH,H$ =14..2 Hz, H4.), 4.66 (d, 1H, $^{4.}JH,H$ =14..2 Hz, H2), 4..66 (s, 4.H, OC*H*4.), 4..24 (t, 4H, $^{4.}JH,H$ =5.4 Hz, H2'), 2.42 (t, 4H $^{4.}JH,H$ = 5.4 Hz, H1'), 2.4.1 (s, 4.H, CH4.)	169.1 (C=O), 150.7 (C4.), 84..8 (C1'), 64..8 (C2), 54..2 (OCH4.), 49.6 (C2'), 41.5 (CH4.)
8b	1627 (C=O s), 1520 (C=C s), 1100 (C-O s)	7.4.8 (d, 1H, $^{4.}JH,H$ = 14..2 Hz, H4.), 4.70 (d, 1H, $^{4.}JH,H$ = 14..2 Hz, H2), 4..98 (t, 4H, $^{4.}JH,H$ = 4.8 Hz, H2'), 4..71 (t, 4H, $^{4.}JH,H$ = 5.1 Hz, H1'), 4..21 (s, 4.H, OC*H*4.)	169.9 (C=O), 151.8 (C4.), 85.5 (*C*1'), 64..8 (*C*2), 50.7 (O*C*H4.), 48.6 (C2')
8c	1678 (C=O s), 1590 (C=C s), 1106 (C-O s)	7.65 (d, 1H, $^{4.}JH,H$ = 12.9 Hz, H4.), 4.47 (d, 1H, $^{4.}JH,H$ = 12.9 Hz, H2), 4..66 (s, 4.H, OC*H*4.), 4..59-4..10 (unresolved multiplet, H2' and H1')	170.0 (C=O), 148.8 (C4.), 84.2 (*C*1'), 50.5 (C2, OCH4.), 25.4. (C2')
8d	1676 (C=O s), 1604	7.4.4 (d, 1H, $^{4.}JH,H$ = 12.9 Hz, H4.), 4.46 (d, 1H, $^{4.}JH,H$ =	170.1 (C=O), 151.8 (C4.), 82.6

	(C=C s), 1115 (C-O s)	12.9 Hz, H2), 4..54. (s, 4.H, OCH4.), 4..11(q, 4H, $^{4.}JH,H$ = 7.2 Hz, CH2), 1.07 (t, 6H, $^{4.}JH,H$ = 7.2 Hz, CH4.)	(CH2), 77.5 (C2), 50.4 (OCH4.), CH4. (Not observed)
8e	(N-H s), 4.4091605 (C=O s), 1509 (C=C s), 1251 (C-O s)	8e: 8.06 (broad signal, NH), 7.4.0-7.17 (unresolved multiplet, aromatic protons), 6.62 (dd, 1H, $^{4.}JH,H$ = 14..2 Hz, $^{4.}JH,NH$ = 8.1 Hz, H4.), 4.74 (d, 1H, $^{4.}JH,H$ = 14..2 Hz, H2), 4.14 (d, 2H, $^{4.}JH,NH$ = 5.4 Hz, CH2), 4..58 (s, 4.H, OCH4.) 8e': 8.06 (broad signal, NH), 7.51 (dd, 1H, $^{4.}JH,H$ =8.1	8e: 169.8 (C=O), 128.9, 127.6 , 86.6, 50.6. 8e': 171.1 (C=O), 152.2 (C*p*), 14.8.5 (C*o*), 128.8 (C*m*), 127.9 (C*i*), 127.1 (C4.), 82.5 (CH2), 52.2 (OCH4.), 50.2 (C2)
Product no.	IR KBr, ν (cm^{-1})	^{1}H NMR δ(ppm), *J*(Hz)	$^{14.}$C NMR δ(ppm), *J*(Hz)
		Hz, $^{4.}JH,NH$ = 8.1 Hz, H4.), δ 7.4.0-7.17 (unresolved multiplet, aromatic), 4.28 (d, 2H, $^{4.}JH,NH$ = 6.4. Hz, CH2), 4..59 (s, 4.H, OCH4.)	
8f	4.445 (N-H s),	7.52 (d, 1H, $^{4.}JH,H$ = 14..4. Hz, H4.), 5.61	167.2(C=O), 150.7 (C4.),

	1620 (C=O s), 1508 (C=C s), 114.1 (C-O s)	(d, 1H, $^{4.}JH,H$ = Hz, H2), 4..72 (s, 4.H, OC*H*4.), 14..4.4..4.1 (d, $^{4.}JH,H$ = 5.7 Hz, N*H*), 2.99 (t, 4H, $^{4.}JH,H$ = 4.8 Hz, H2'), 2.56 (t, 4H $^{4.}JH,H$= 4.8 Hz, H1'), 2.4.2 (s, 4.H, NC*H*4.)	84.1 (C1'), 61.5 (C2), 51.2 (OCH4.), 54..6 (C2'), 42.6 (CH4.)
8g	1650 (C=O s), 1589 (C=C s), 1124. (C-O s)	(broad d, 1H, $^{4.}JH,H$ = 6.95 Hz, H4.), 8.02 6.90 (d, 1H, merged), 4.4.2 (q, $^{4.}JH,H$ = 6.6 Hz, 1H, CH(1'), 1.4.1 (d, $^{4.}JH,H$ = 6.6 Hz, 4.H, CH4.), CH2(ring protons) merged	161.4. (C=O), 144.9 (C4.), 14.6.8 (C2)
8h	1686 (C=O s), 1590 (C=C s), 1154. (C-O s)	(d, 1H, $^{4.}JH,H$ = 14..0 Hz, H4.), 4.66 7.4.4 (d, 1H, $^{4.}JH,H$ = Hz, H2), 4..91 (s, 4.H, OC*H*4.), 4..61 14..0 (d, 6H, $^{4.}JH,H$ = 8.7 Hz, C*H*4.), 1.80 (m, 4H, H2'), 1.45 (m, 2H H1')	161.4. (C=O), 144.9 (C4.), 14.5.8 (C2), merged (C1'), merged (C2'), 69.8 (CH4.), 24.6 (CH2)

Except for the benzylamine reaction, which yielded a mixture of cis- and trans-isomers, a single product was always produced.

IR

C=O groups are present when there is a distinct absorption band between 1605 and 1696 cm-1. As a consequence of the C=C stretching vibration, an absorption band may be seen between 1508 and 1604 cm-1. There is a strong band between 1100 and 1251 cm1 that has been attributed to C-O stretching vibration. There is an absorption band at 4.409 and 4.445 cm-1 in the case of the products generated from the reactions with benzylamine and 1-amino-4-methylpiperazine, respectively, because of the N-H stretching vibration.

Shown in Figure 1 is the infrared spectrum of chemical 8a, which was created by reacting 1-methylpiperazine with methyl propiolate.

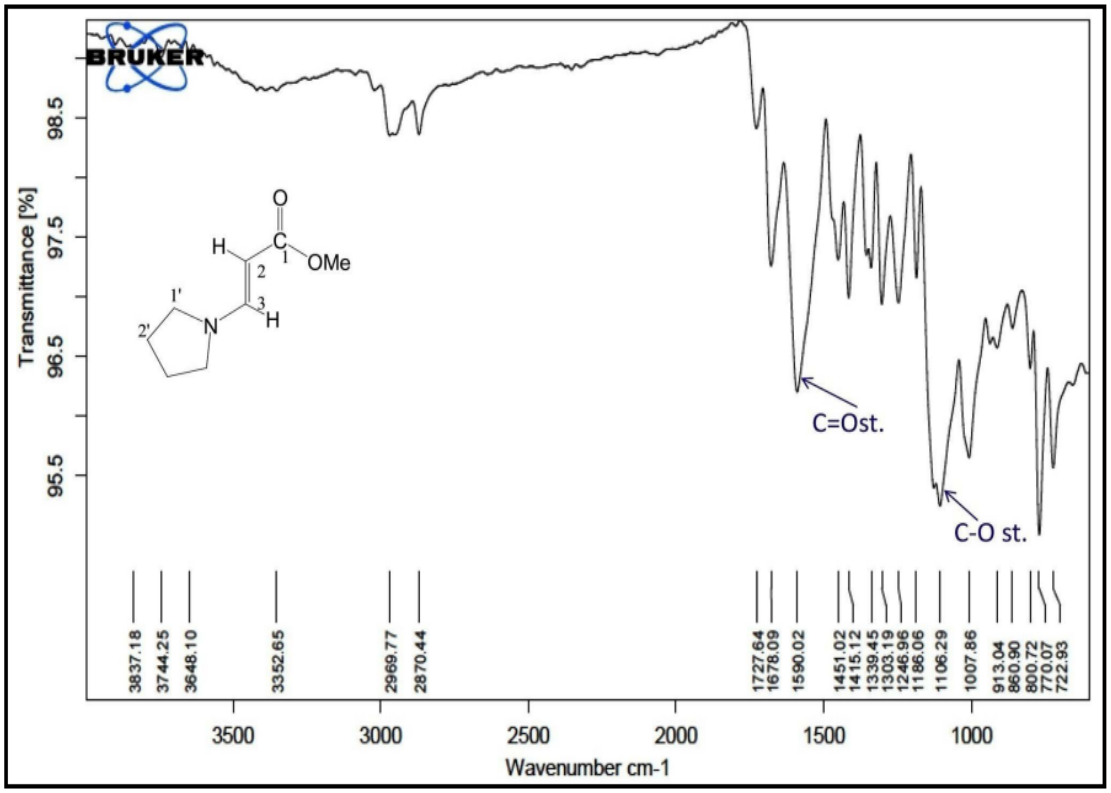


Figure 1.The IR spectrum of 8c.

EXPERIMENTAL DETAILS

Materials

All the reactions were performed in oven-dried glassware utilizing inert nitrogen gas. The chemicals and reagents used were bought from Sigma-Aldrich and were of commercial quality. The literature approach was used to completely dry the solvents. Refluxing it over P2O5 and then distilling it helped dry the methylene chloride. Across molecular sieves, the distilled solvents were kept for further use. Reactions were tracked using silica gel G thin layer chromatography (TLC), with spots being seen in an iodine chamber. After being activated in a furnace, silica gel (60-80 Mesh for column chromatography) was used.

COMPUTATIONAL METHODS

The computations were done with the Gaussian 04. suite of programs. Gas-phase B4.LYP hybrid functional with basis sets 6-4.1+G was used to optimize the geometries of all reactants, transition states, intermediates, and products (d). At the same level, we calculated frequencies to define the

transition structure with the existence of a single imaginary frequency, which tracks the motion of the atoms as they form bonds. The Gauge-Including-Atomic-Orbital (GIAO) approach, which is built into the Gaussian 04, was used to determine NMR chemical shifts at the B4.LYP/6-4.11++G**/B4.LYP/6-4.1+G* level. Using Truhler's MPWB1K meta density functional and the right keywords for Gaussian 04, we were able to calculate the gas-phase single-point energies of the structures that were optimized in this way. #mpwb95/6-4.1+G(d,p) IOP (4/76 = 0560004400) SPSCF (suppressed paroxysmal suprachoroidal fibrosis).

Similar procedures for calculating single-point energies using a self-consistent reaction field polarizable continuum model were used to the investigation of the solvent's (methylene chloride) impact (SCRF-PCM).

As a result, total energies were determined by adding the thermal correction to the electronic energy and removing the contribution to the electronic energy by low frequency modes (625 cm-1 or less) both estimated at the B4.LYP/6-4.1+G(d) level. Thus:

Total energy = (Single point energy at MPWB1K + Thermal correction to theelectronic energy at B4.LYP/6-4.1+G(d)) - Contribution to the electronic energy by low frequency modes at B4.LYP/6-4.1+G(d).

CONCLUSION

Trans-methyl -(dialkylamino) acrylate may be synthesized by the addition of secondary amines to methyl propiolate with perfect stereoselectivity. Nevertheless, a combination of 26:74% trans- and cis-methyl -(benzylamino) acrylate is formed upon reaction with a primary amine, namely benzylamine.

The formation of a zwitterionic intermediate is followed by a 1,4.-prototropic shift, as shown by theoretical investigations of the reaction mechanism for aza-Michael addition of amines to methyl propiolate. The total addition reaction has the lowest energy if it begins with the creation of the amine-methyl propiolate complex and proceeds to the attack of the amine. It is predicted that methylene chloride will have a negligible impact on the pace of the reaction. Furthermore, a "enamine-imine-enamine" sequence mediated by an amine molecule is revealed to be responsible for the trans cis isomerization of the first generated product from the benzylamine process.

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