Structural Chemistry
https://doi.org/10.1007/s11224-021-01735-9

ORIGINAL RESEARCH

Michael addition of ethyl anthranilate and phenyl monothioanthranilate to acetylenic esters: experimental and theoretical results

Pratibha Sharma[1] · Raakhi Gupta[1] · Raj K. Bansal[1]

Received: 21 December 2020 / Accepted: 15 January 2021

Abstract

The reaction of ethyl anthranilate with DMAD and with methyl propiolate in dichloromethane in the presence of ethylaluminium dichloride as catalyst at room temperature gives a mixture of the respective *E*- and *Z*-intermediate derivatives which do not cyclize even on refluxing for several hours. On carrying out the reaction in refluxing methanol in the absence of the catalyst, only one stereochemical isomer is obtained which is *Z*-intermediate indicating conversion of less stable isomer into the thermodynamically more stable derivative under these conditions. The resulting product did not cyclize even on refluxing in methanol in the presence of montmorillonite K10 clay catalyst. The reaction of phenyl monothioanthranilate with DMAD and with methyl propiolate gives similar results. A theoretical investigation of the reaction of ethyl anthranilate with methyl propiolate at the B3LYP/6-31 + G(d) level reveals that it occurs in five steps.

Keywords Michael addition · Ethyl anthranilate · Phenyl monothioanthranilate · DMAD · Methyl propiolate · DFT calculations

Introduction

The Michael reaction though discovered in the year 1887 [1, 2] continues to attract attention of the chemists owing to its versatility in organic synthesis [3–6]. The aza-Michael reaction involving addition of amines and related nitrogen compounds makes a variety of β–amino carbonyl compounds accessible, which are important synthons for obtaining bioactive natural motifs [7–10] and chiral auxiliaries [11–13]. Michael addition of amines to acetylenecarboxylic acid derivatives has been studied for its mechanistic [14–16] and synthetic [17–19] aspects. We recently reported our experimental and theoretical results about the addition of primary and secondary amines to DMAD [20] and maleic anhydride [21]. In the former case, we succeeded for the first time in isolating and characterizing the intermediate, dimethyl 2-(*N*-benzylamino)butane-1,4-dicarboxylate generated from the reaction of benzylamine with DMAD, thereby confirming the reaction mechanism predicted by theoretical calculations [20].

The reaction of aromatic amines with DMAD under thermal condition has been reported to give 4(1H)-quinoline derivatives [22]. Similarly, ethyl anthranilate on refluxing with DMAD in methanol followed by heating under vacuum at ~ 250 °C gave 8-carbethoxy-2-carbomethoxy-4-(1H)-quinolone (Scheme 1) [23].

We were motivated to reinvestigate the above reaction experimentally and theoretically with three objectives: to isolate the initially formed *E*- or/and *Z*-intermediate(s) by carrying out the reaction in a less polar solvent, to attempt accomplish it under milder conditions with the use of a catalyst, if necessary and to know the reason of regioselectivity in cyclization. Furthermore, we carried out a similar reaction of phenyl monothioanthranilate with methyl propiolate and with DMAD under similar conditions to observe difference, if any, in the mode of cyclization. We expected that theoretical investigation would reveal the reason of the cyclization occurring at high temperature.

Experimental details

General

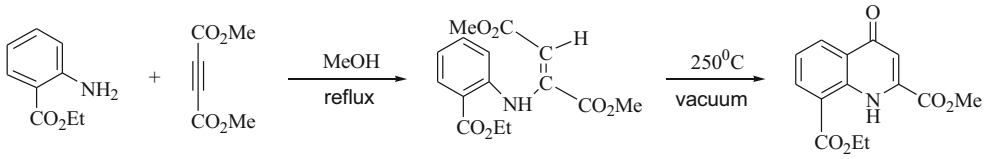
Commercially available ethyl anthranilate, methyl propiolate, and DMAD were purchased from Merck and used without

✉ Raakhi Gupta
raakhi27@yahoo.com

[1] Department of Chemistry, IIS (deemed to be University), Jaipur 302020, India

Published online: 29 January 2021

Scheme 1 Reaction of ethyl anthranilate with DMAD



1 **2b** **3b** **4b**

further purification. Ethylaluminium dichloride (1.8 M in toluene) solution was purchased from Sigma-Aldrich. Phenyl monothioanthranilate was prepared according to the literature method [24]. IR spectra were recorded on Brucker spectrometer in KBr pellet. NMR spectra were recorded in $CDCl_3$ on Jeol-400 MHz spectrometer, ^1H NMR at a frequency of 399.78 MHz, and ^{13}C NMR at a frequency of 100.53 MHz using TMS as the internal reference. The C, H, N elemental analyses were done on a FLASH Ea 1112 series CHN analyzer.

Reaction of ethyl anthranilate with methyl propiolate in methylene chloride in presence of ethylaluminium dichloride as catalyst

Methyl propiolate (3.4 mmol, 284 mg, 0.3 mL) was dissolved in CH_2Cl_2 (10 mL) taken in a 25 mL RB flask at r.t. under nitrogen atmosphere. To this solution was added $EtAlCl_2$ (1.8 mmol, 217mg, 190 μL of 1.8 M solution in toluene) when yellow to orangish brown colour developed. After stirring it for about 30 min. at r.t., a solution of ethyl anthranilate (3.4 mmol, 558 mg, 0.5 mL) in CH_2Cl_2 (2 mL) was added dropwise and the reaction mixture was stirred at r.t. for 36 h, progress of the reaction being monitored by TLC (solvent: pet ether 60-80°C EtOAc: 3:1 v/v). After completion of the reaction, the reaction mixture was quenched with distilled water (30 mL) followed by the addition of NH_4OH until it became neutral. The organic layer was separated with the separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The CH_2Cl_2 extracts were mixed, dried over anhydrous sodium sulfate and the solution was concentrated to ~2 mL. The crude product on column chromatography over silica gel-eluent: pet ether 60–80 °C EtOAc: 9:1 v/v afforded a white crystalline product.

A similar procedure was followed for the reaction of ethyl anthranilate (13.5 mmol, 2234mg, 2 mL) with DMAD (13.5 mmol, 1965mg, 1.7 mL) in the presence of ethylaluminium dichloride as catalyst.

Reaction of ethyl anthranilate with DMAD/methyl propiolate in methanol in the absence/presence of montmorillonite K10 clay catalyst

Ethyl anthranilate (7.0 mmol, 1170 mg, 1 mL,) was dissolved in methanol (5 mL) and taken in a 25 mL RB flask at r.t.. To this was added 1 equiv. of DMAD (6.7 mmol, 959 mg, 830 μL) dissolved in 8 mL of methanol dropwise at r.t. with continuous stirring. The reaction mixture was then refluxed for 2 h. The progress of the reaction was monitored by TLC (solvent: pet ether 60–80 °C:EtOAc: 7:3 v/v). After the reaction was complete, the reaction mixture was concentrated and a few drops of diethyl ether were added and kept in refrigerator. A viscous mass was obtained, which was separated and dried under vacuum.

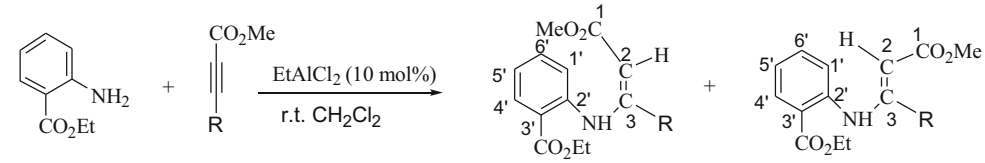
Similar procedure was followed for the reaction of ethyl anthranilate (7.0 mmol, 1170 mg, 1.0 mL) with methyl propiolate (6.7 mmol, 567 mg, 0.6 mL).

The above experiments were repeated under similar conditions in the presence of montmorillonite K10 clay (10 mol%).

Reaction of phenyl monothioanthranilate with DMAD/methyl propiolate in methanol

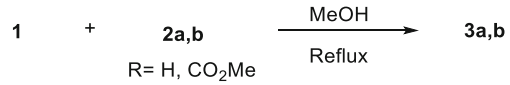
Phenyl monothioanthranilate (0.40 mmol, 100 mg) was dissolved in methanol (5 mL) taken in a 25 mL RB flask at r.t.. To this was added 1 equiv. of DMAD (4.3 mmol, 620 mg, 0.53 mL) dissolved in 10 mL of methanol dropwise at room temperature with continuous stirring. The reaction mixture

Scheme 2 Reaction of ethyl anthranilate with methyl propiolate and with DMAD in the presence of catalyst



1 **2** **3a,b** **5a,b**

	a	b
R	H	COOMe



Scheme 3 Reaction of ethyl anthranilate with methyl propiolate and with DMAD in methanol

was then refluxed for 6 h. The progress of the reaction was monitored by TLC (solvent: pet ether 60-80°C:EtOAc: 8:2 v/v). After the reaction was complete, solvent was removed under vacuum and the residue was distilled under reduced pressure.

Similar procedure was followed for the reaction with methyl propiolate, but in this case, product was isolated by column chromatography and solvent was removed under vacuum.

The above experiments were repeated under similar conditions in the presence of montmorillonite K10 clay (10 mol%).

Computational methods

Gaussian 16 suite of programs was used for all calculations [25].

Geometries of the reactants, transition structures, intermediates, and the products involved in the model reaction were optimized in the gas phase at the B3LYP/6-31 + G(d) level of theory. Frequency calculations were done at the same level to characterize the energy minimum or the first saddle point in the presence of no imaginary and only one imaginary frequency, respectively.

The intrinsic reaction coordinate (IRC) calculations [26, 27] starting from the transition structure were carried out at the same theory level to confirm its relation to the respective reactants and the intermediate/product. The total enthalpy was calculated by adding thermal corrections to the sum of the electronic and thermal enthalpy. The free energy ΔG at a temperature of 298.15 K was calculated as follows:

$$\Delta G = \Delta H - T\Delta S$$

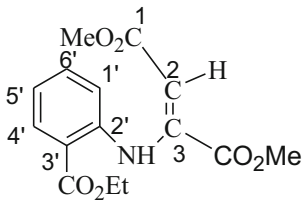
ΔH = relative enthalpy
ΔS = relative entropy
T = 298.15 K

Results and discussion

Experimental results

Ethyl anthranilate did not react with DMAD in dichloromethane even on refluxing for several hours. In view of many reports about the use of organometallic complexes as catalysts for the addition of aromatic amines to different Michael acceptors [28, 29], ethyl anthranilate was reacted with methyl propiolate (2a) and with DMAD (2b) in the presence of $EtAlCl_2$ as catalyst in dichloromethane at r.t. when a smooth

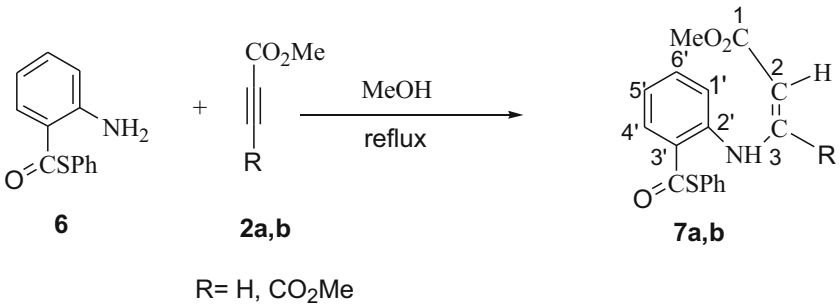
Table 1 The ^{1}H NMR chemical shift values of 3b reported earlier [23] and the values obtained in present investigations. [a]Originally reported on the scale of τ



3b

	^{1}H NMR Chemical shifts (δ)	
	Present studies ($CDCl_3$)	**Reported earlier**[a] ($CDCl_3$)
N-H, 1H	11.42	11.71
Ph, 4H	6.64 - 7.32	7.01-8.38
H-2, 1H	5.58	5.47
OCH_2CH_3,2H	4.41	4.68
C-1 OMe, 3H	3.88	3.89
C-3 OMe, 3H	3.81	3.82
OCH_2CH_3, 3H	1.41	1.43

Scheme 4 Reaction of phenyl monothioanthranilate with methyl propiolate and with DMAD in methanol



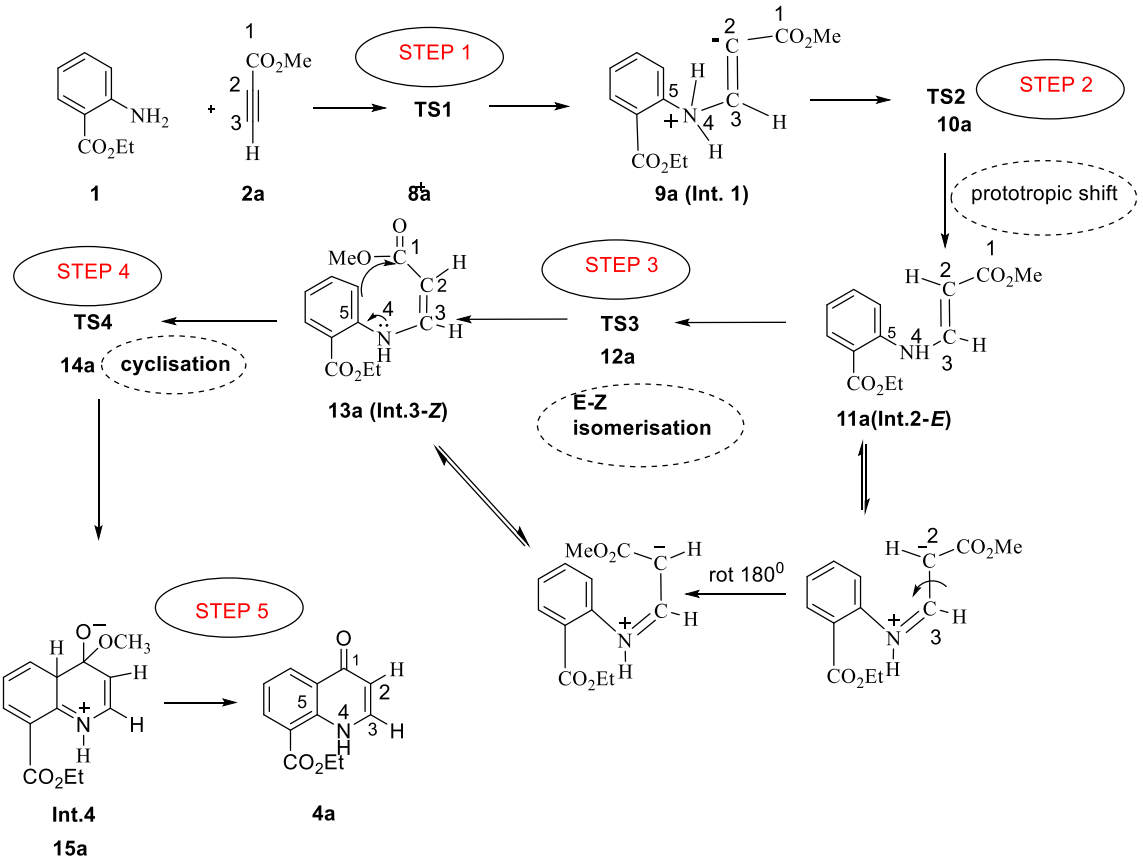
reaction occurred to afford white crystalline products in moderate yields (Scheme 2).

The reaction did not proceed further even on prolonged refluxing under the above conditions. Furthermore, no change occurred on refluxing in toluene also.

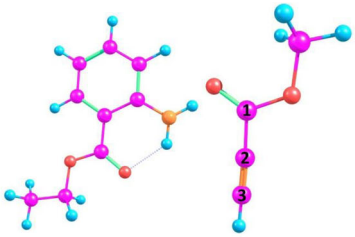
As revealed by ^{1}H NMR spectra, in each case a mixture of *Z*- and *E*- products is formed, which, however, could not be separated, but it could be possible to determine the relative percentages of the two isomers in each case on the basis of the relative intensities of the ^{1}H NMR signals of the vinylic proton(s). The percentage of the Z-isomer having intramolecular hydrogen bonding between the N-H proton and the ester group is much higher, which may be attributed to its greater thermodynamic stability.

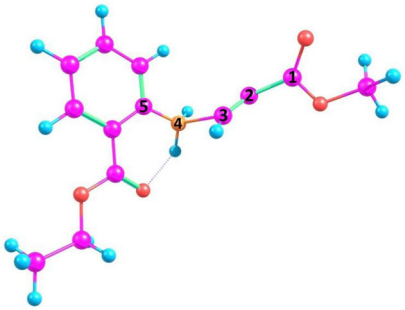
These results are in accordance with our earlier report wherein we described in detail the results of the Michael reaction of primary and secondary amines with DMAD; secondary amines give a single product whereas reaction with a primary amine leads to the formation of a mixture of the *Z*- and *E*-isomers, the former being formed as the major product [20].On investigating the mechanism of isomerization of the initially formed *E*-isomer to the Z-isomer theoretically, it was found that the proton on the nitrogen atom is reversibly transferred to the C2 atom through a bridge formed by a second molecule of the amine followed by successive rotation about the C2–C3 bond and transfer of the proton back to the N atom [20].

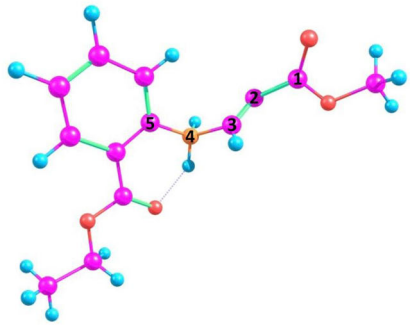
All the products could be well characterized on the basis of the IR, ^{1}H NMR and ^{13}C spectral studies. In the IR spectra, an



Scheme 5 Model reaction of ethyl anthranilate with methyl propiolate computed at the B3LYP/6-31 + G(d) level







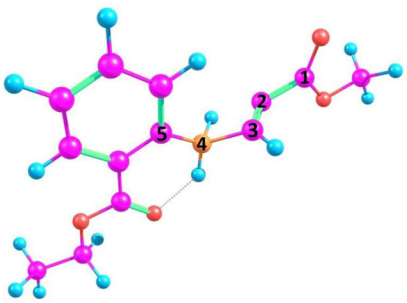
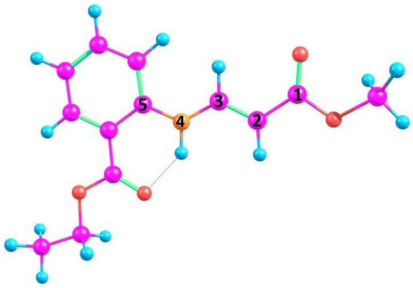
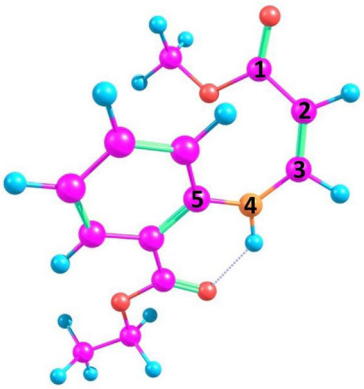


Fig. 1 Geometries of different species involved in the reaction of ethyl anthranilate with methyl propiolate optimized at the B3LYP/6-31 + G(d) level





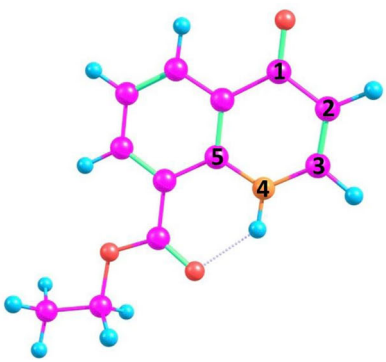


Fig. 1 (continued)

absorption band of moderate intensity at ~ 3250–3450 cm^{-1} results due to the N–H stretching (st.) vibration. Besides, intense absorption bands in the regions of 1615–1735 cm^{-1} (C=O st.) and 1100–1270 cm^{-1} confirm the ester groups.

In the ^{1}H NMR spectrum, the characteristic chemical shifts and the multiplicities of the signals resulting due to the vinylic protons (=C–H) confirmed the presence of the *Z*- and *E*-isomers in each case. For example, in the ^{1}H NMR spectrum of the

Table 2 Total enthalpy and entropy of different species computed at the B3LYP/6-31 + G(d) level

Entry	Total enthalpy in au	Entropy(calK^{-1} mol^{-1})
1	− 554.428224	105.507
2a	− 305.059551	78.643
8a (TS1)	− 859.443772	144.796
9a (Int.1)	− 859.444182	143.877
10a (TS2)	− 859.437333	141.758
11a (Int.2-*E*)	− 859.554599	141.715
12a (TS3)	− 859.478704	140.751
13a (Int.3-*Z*)	− 859.537430	139.401
4a	− 743.939056	116.599
MeOH	− 115.614075	56.858

product obtained from the reaction of ethyl anthranilate with methyl propiolate, a doublet at δ 2.59 (H2) and a double doublet (dd) at δ 4.20 ppm (H3) with a large coupling constant ($^3J_{HH}$ = 13.6 Hz) confirm the *E*-isomer (**5a**), whereas another set of a doublet at δ 2.56 (H2) and a dd at δ 4.70 (H3) with a comparatively smaller coupling constant ($^3J_{HH}$ = 8.0 Hz) is in accordance with the *Z*-isomer (**3a**). It is noteworthy that the NMR signal for the H2 is much upfield than that for the H3, which may be attributed to the +M effect of the nitrogen lone pair. Another distinguishing feature of the ^{1}H NMR spectra of the *Z*- and *E*-isomers is the chemical shift of the N–H proton: in the former, it is much downfield (δ ~ 12 ppm) and broadened due to the intramolecular hydrogen bonding, whereas in the latter, it is upfield (δ ~ 11 ppm) and sharper. The detailed physical and spectral data are given in the Supplementary Material.

On refluxing an equimolar solution of ethyl anthranilate and methyl propiolate/DMAD in methanol, a single product (**3a**,**b**) was formed in each case, as reported earlier [23], indicating complete change of the *E*-isomer into the *Z*-isomer (Scheme 3).

The products could be well characterized on the basis of IR and NMR studies.

As mentioned earlier, the product **3b** formed from the reaction of ethyl anthranilate with DMAD was reported by George and co-worker [23]. The ^{1}H NMR chemical shift values of the compound reported earlier [23] and the values obtained by us are given in Table 1.

It may be noted that the chemical shift values obtained in the present investigation accord well with the values reported earlier.

Clays have been extensively used as catalysts in a variety of organic reactions including Michael additions [30, 31]. A montomorillonite K10 clay catalyzed Michael type addition of aniline derivatives to cinnamaldehyde followed by intramolecular cyclization was reported [32]. In another report, trisubstituted pyridines were obtained from a montomorillonite K10 clay catalyzed three-component reaction of enaminones, β-ketoesters/1,3-diketones, and ammonium acetate in boiling isopropyl alcohol [33]. In view of this, an equimolar solution of ethyl anthranilate and methyl propiolate in methanol was refluxed in the presence of montomorillonite K10 (10 mol%); the reaction, however, did not proceed further after the formation of **3a** as revealed by the TLC.

On refluxing an equimolar solution of phenyl monothioanthranilate (**6**) and methyl propiolate/DMAD in methanol, a single product (**7a,b**) was formed in each case (Scheme 4).

In this case also, initially formed product did not cyclize even on refluxing in methanol in the presence of montomorillonite K10 for prolonged period.

The products so formed could be well characterized on the basis of IR and NMR spectral studies.

Theoretical results

With a view to investigate the mechanism of the reaction, we computed a model reaction of ethyl anthranilate with methyl propiolate at the DFT level (Scheme 5).

Scanning of the potential energy surface reveals that the reaction occurs in five steps.

The first step involving the attack of ethyl anthranilate on methyl propiolate leads to the formation of a zwitterionic intermediate (**9a Int. 1**). It is followed by a 1,3-prototropic shift of the NH proton to form the *E* **Int.2 (11a)**. The latter has nitrogen lone pair conjugated with the C=C bond due to which C2-C3 bond acquires a single bond character and rotation about it becomes possible. Thus in the third step, the *E* intermediate **Int.2** changes into the *Z* **Int.3**. As will be seen later, it is a high energy path, but much greater thermodynamic stability of the *Z* **Int.3** (**13a**) makes it possible. The next step

Table 3 Thermodynamic data of different steps of Michael addition of ethyl anthranilate to methyl propiolate

Step	$\Delta H^{\#}$ (kcal mol^{-1}) [a]	$\Delta S^{\#}$ (cal mol^{-1} K^{-1}) [b]	$\Delta G^{\#}$ (kcal mol^{-1}) [c]	ΔH^{o} (kcal mol^{-1}) [d]	ΔG^{o} (kcal mol^{-1}) [f]
1	27.61	− 39.35	39.34	27.35	39.27
2	4.30	− 2.11	4.93	− 68.88	− 68.14
3	47.22	− 0.42	47.51	10.37	11.03
Overall reaction energy	-	-	-	− 41.02	-37.82

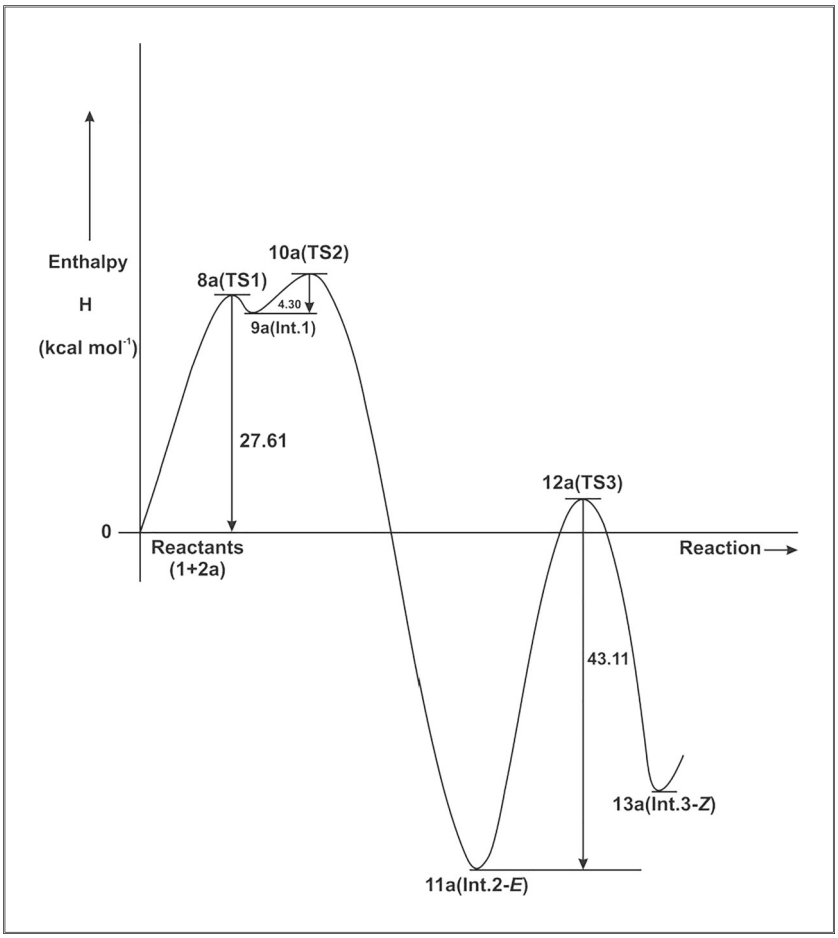


Fig. 2 Energy profile diagram followed by addition of ethyl anthranilat with methyl propiolate

involves intramolecular cyclization to form **Int.4**(**15a**); the transition structure (**14a**) involved in this cyclization, however, could not be located. The intermediate **Int.4** splits off a CH_3OH molecule to give the final product 4-(1H)-quinolone derivative (**4a**).

Optimized geometries

The optimized geometries of different species involved in the reaction of ethyl enthranilate with methyl propiolate are presented in Fig 1.

Energetics

The thermodynamic data of different species and the relative enthalpies and free energies of different steps of the aza-Michael addition of ethyl anthranilate to methyl propiolate are presented in Tables 2 and 3 respectively.

The energy profile diagram depicting the enthalpy and free energy changes in the reaction of ethyl anthranilate **1**with methyl propiolate **2a** is presented in Fig. 2.

Overall, the reaction is exergonic, ΔG^0 being − 37.82 kcal mol. It will provide sufficient energy to overcome the high free energy barrier of steps 1 and 3. Thus, apparently, it appears that the third step is the rate determining, but in practice, the first step will be rate determining. To initiate the first step, whose activation free energy is high, $\Delta G^{\#}$ (39.34 kcal mol^{-1}), external energy is required. This is in consonance with the experimental results, where the reaction takes place on refluxing the reaction mixture in methanol.

Conclusions

The polarity of the solvent plays a crucial role in the Michael reaction of ethyl anthranilate with acetylenic esters. The reaction in a less polar solvent, namely dichloromethane, occurs only on refluxing in the presence of an organoaluminium catalyst to yield a mixture of the *E*- and *Z*-intermediate derivatives. However, on refluxing the reactants in methanol, reaction occurs without the aid of a catalyst forming only the thermodynamically more stable *Z*-isomer; thus, the initially formed E-intermediate changing into the *Z*-isomer under these conditions, but the latter does not cyclize even on refluxing the reactants in methanol in the presence of montomorillonite K10 catalyst.

Similar results are obtained on reacting phenyl monothioanthranilate with methyl propiolate and with DMAD under similar conditions.

A theoretical investigation of the model reaction of ethyl anthranilate with methyl propiolate at the DFT level rationalizes the experimental results, particularly the high temperature to accomplish the reaction.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11224-021-01735-9.

Funding This study is funded by the IIS (deemed to be University), Jaipur (India).

Data availability All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Compliance with ethical standards

Competing interests The authors declare no competing interests.

References

1. Michael A (1887). J Prakt Chem 3:349
2. Michael A (1887). J Am Chem Soc 9:112
3. Jung ME (1991) In: Trost BM, Fleming I (eds) Comprehensive organic synthesis, vol 4. Pergamon, Oxford, pp 1–67
4. Perlmutter P (1992) Conjugate addition reactions in organic synthesis In: Tetrahedron Organic Chemistry Series, Vol. 9. Pergamon, Oxford, p 114
5. Shibasaki M, Sasai H, Arai T (1997). Angew Chem Int Ed 36:1236
6. Gellman S (1998). Acc Chem Res 31:173
7. Nicolaou KC, Dai WM, Guy RK (1994). Angew Chem Int Ed Engl 33:15
8. Frackenpohl J, Arridson PI, Screiber JV, Seebach D (2001). Chem Biol Chem 2:445
9. Liu M, Sibi MP (2002). Tetrahedron 58:7991
10. Cardillo G, Tomasini C (1996). Chem. Soc. Rev 25:117
11. Eliel EL, He XC (1990). J Org Chem 55:2114
12. Hayashi Y, Rode JJ, Corey EJ (1996). J Am Chem Soc 118:5502
13. Genov M, Dimitrov V, Ivanova V (1997). Tetrahedron: asymmetry 8:3703
14. Huisgen R, Herbig K, Siegl A, Hurber H (1966). Chem Ber 99: 2546
15. Ziyaei-Halimehjani A, Saidi MR (2008). Tetrahedron Lett 49:1244
16. Dąbrowski J, Terpiński J (1965). Tetrahedron Lett 6:1363.
17. Yavari I, Souri S (2007). Synlett:2969
18. Yavari I, Souri S (2008). Synlett:1208
19. Hadjebi M, Hashtroudi MS, Bijanzadeh HR, Balalaie S (2011). Helv Chim Acta 94:382
20. Gurjar A, Poonia P, Sinha P, Bansal RK (2014). Tetrahedron Lett 55:2504
21. Kour M, Gurjar R, Bansal RK (2017). Aust J Chem 70:1247
22. Heindel ND, Bechara IS, Lemke TF, Fish VB (1967). J Org Chem 32:4155
23. Khetan SK, Hiriyakkanavar JG, George MV (1968). Tetrahedron 24:1567
24. Staiger RP, Miller EB (1959). J Org Chem 24:1214
25. Gaussian 16, Revision C.01, Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Petersson GA, Nakatsuji H, Li X, Caricato M, Marenich AV, Bloino J, Janesko BG, Gomperts R, Mennucci B, Hratchian HP, Ortiz JV, Izmaylov AF, Sonnenberg JL, Williams-Young D, Ding F, Lipparini F, Egidi F, Goings J, Peng B, Petrone A, Henderson T, Ranasinghe D, Zakrzewski VG, Gao J, Rega N, Zheng G, Liang W, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Throssell K, Montgomery JA Jr, Peralta JE, Ogliaro F, Bearpark MJ, Heyd JJ, Brothers EN, Kudin KN, Staroverov VN, Keith TA, Kobayashi R, Normand J, Raghavachari K, Rendell AP, Burant JC, Iyengar SS, Tomasi J, Cossi M, Millam JM, Klene M, Adamo C, Cammi R, Ochterski JW, Martin RL, Morokuma K, Farkas O, Foresman JB, Fox DJ (2016) Gaussian, Inc., Wallingford CT.
26. Gonzalez C, Schlegel HB (1989). J Chem Phys 90:2154
27. Gonzalez C, Weinhold F (1990). J Chem Phys 94:5523
28. Kawatsura M, Hartwig JF (2001). Organometallics 20:1960
29. Fadini L, Togni A (2003). Chem Commun 30:30
30. Dasgupta S, Török B (2008). Org Prep Proced Int 40:1
31. Ranu BC, Chattopadhyay K (2009). Green procedure for the synthesis of useful molecules avoiding hazardous solvents and toxic catalysts In Eco-friendly synthesis of fine chemicals, Ballini R (ed.), Royal Society of Chemistry, Cambridge, pp 186-219.
32. D Paolis O, Teixeira L, Török B (2009). Tetrahedron Lett 50:2939
33. Reddy GJ, Latha D, Thirupathiah C, Rao KS (2005). Tetrahedron Lett 46:301