Tetrahedron 70 (2014) 3284–3290

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Formal aza-[3+3] versus aza-[3+2] cycloadditions of heterocyclic enaminones with maleic anhydride and maleimides: skeletally diverse synthesis of pyrrolizidinones, indolizidinones, and pyrroloazepinones

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ARTICLE INFO

Article history:
Received 3 September 2013
Received in revised form 11 October 2013
Accepted 23 October 2013
Available online 29 October 2013

Keywords:
Enaminone
Heterocycle
Azaanulation
1-Azabicycles
Alkaloid-like

ABSTRACT

The domino aza-annulation of cyclic enaminones with maleic anhydride and maleimides was investigated, and selectively one-step skeletally diverse synthesis of each alkaloid-like pyrrolizidinone, indolizidinone, and pyrrolo[1,2-*a*]azepinone was developed, switching between aza-[3+3] and aza-[3+2] modes of formal cycloaddition reactions. For the synthesis of pyrroloazepinones, seven-membered enaminone and maleic anhydride or maleimides are efficient, via the [3+2] mode. To access indolizidinones, five or six-membered enaminones are the choice, and both [3+2] and [3+3] modes were viable exclusively with maleic anhydride. Pyrrolizidinone can be selectively synthesized in good yield through the [3+2] mode, only with five-membered enaminone and *N*-(4-NO_2Ph)maleimide, under catalysis by PTSA.

1. Introduction

Fused bicyclic heterocycles with a bridgehead nitrogen atom are present in various natural and unnatural bioactive compounds. Among these heterocycles, 1-azabicyclo[3.3.0]octanes,[1] 1-azabicyclo[4.3.0]nonanes,[2] and 1-azabicyclo[5.3.0]decanes[3] have been synthesized by diverse approaches because they occur in pyrrolizidines, indolizidines, and pyrroloazepines, which are three important classes of structural scaffolds present in alkaloids and alkaloid analogues with application in medicinal chemistry.[4]

Maleic anhydride and maleimides are easily available and versatile electrophiles whose use in the synthesis of *N*-heterocycles, including 1-azabicycles, is well described.[5,6] A particular synthetic approach involves their direct reaction with an enaminone.[7–18] However, a close analysis of the reactions depicted in Fig. 1 reveals a complex chameleonic behavior of enaminones in the aza-

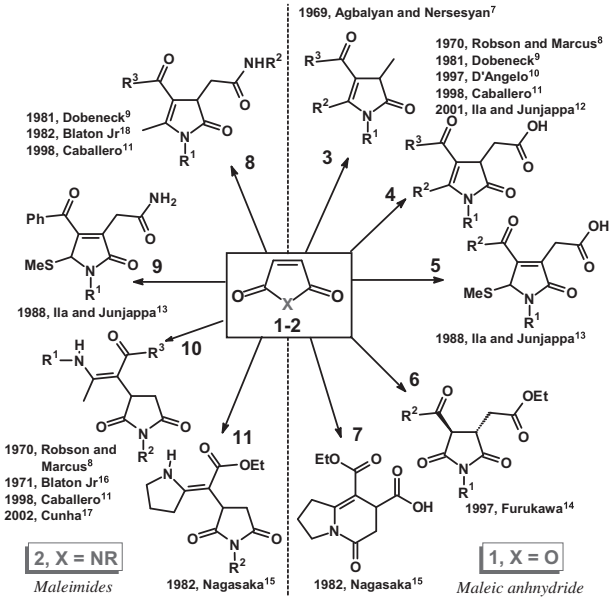

Fig. 1. Reaction of enaminones with maleic anhydride and maleimides.

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http://dx.doi.org/10.1016/j.tet.2013.10.071

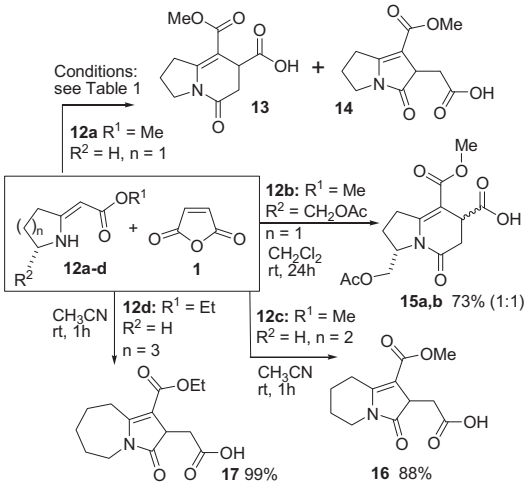
annulations with the studied electrophiles, whereby small variation of the nature of substituents of both enaminone and mentioned electrophiles, may result in significant variation of the double bond position, and in nature of the obtained heterocycle. The 2-pyrrolidone nucleus present in compounds **3**–**5** and **8**,**9**, generated through formal aza-[3+2] cycloaddition, predominated in most of these reactions. The Michael adduct **10** and **11** were observed only in reactions with maleimides, and 3,4-*trans*-disubstituted succinimide **6** was formed only with maleic anhydride, Fig. 1.

The formation of product **7** is remarkable; while acyclic enaminones are prone to react with maleic anhydride through formal [3+2] cycloaddition, the five-membered enaminone provides the indolizidinone **7**, which corresponds to a formal aza-[3+3] cycloaddition. This is the unique example, and somewhat not expected, of such reaction patterns.[15]

Despite the scenario depicted in Fig. 1 represents a significant contribution in the development of concise synthesis of *N*-based heterocycles,[19] the synthetic potential of the formal aza-cycloaddition reactions of heterocyclic enaminones with maleic anhydride/maleimides in the synthesis of densely substituted 1-azabicycles is still under-exploited. Inspired by these facts, we decided to develop a simple and divergent approach adequate to the purpose of synthesize such heterocycles in a quick way, with emphasis on skeletal diversity.[20] This strategy is in connection with our effort devoted to the development of simple one-pot and/or multicomponent synthetic methodologies, which permit direct access of compounds to biological evaluation.[21] One of such approach employs enaminones[22] as building blocks for the synthesis of *N*-heterocycles through formal aza-cycloaddition reactions.[17,23] In this way, we disclosure herein our ongoing study concerning the formal aza-[3+2] and formal aza-[3+3] cycloaddition reactions of cyclic enaminones,[24] including a chiral one, with maleic anhydride and *N*-aryl-maleimides, wherein pyrrolizidinone, indolizidinone, and pyrroloazepinone heterocycles could be selectively obtained.

2. Results and discussion

To gain insight into the synthetic and mechanistic implications in the reactions of maleic anhydride and maleimides with heterocyclic enaminones en route to azabicycles, five, six, and seven-membered enaminone derivatives **12a**–**d** were prepared, including a chiral one.[25] In an initial trial, enaminone **12a** was reacted with maleic anhydride **1** in the condition described by Nagasaka and co-workers for the ethyl ester analogous of **12a**.[15] In this condition, we obtained indolizidinone **13** in good yield, in a mmol scale, Scheme 1 and Table 1 (entry 1).



Scheme 1. Reactions of cyclic enaminones with maleic anhydride.

Table 1
Reaction conditions to the formal aza-cycloaddition of enaminone **12a** and maleic anhydride **1**

Entry[a]	Solvent	Catalyst (mol %)	Yield (%) **13**	**14**
1	Benzene	—	78	—
2	CH_2Cl_2	—	85	—
3	$CHCl_3$	—	15	10
4	CH_3CN	—	85	—
5[b]	CH_3CN	—	81	16
6[c]	CH_3CN	BiI_3 (10)	61	19
7	CH_3CN	BiI_3 (100)	50	36

[a] Reaction carried out 0.1 M in each reagent at rt.
[b] Reaction at reflux.
[c] Reaction carried out 0.6 M using 100 mmol of each reagent at rt.

Formation of the six-membered ring instead of five one, i.e., indolizidinone **13** versus pyrrolizidinone **14** (corresponding to formal aza[3+3] instead of aza[3+2] cycloaddition) with the five-membered enaminone **12a** is not well understood, because in all described reactions of acyclic enaminones with maleic anhydride the 2-pyrrolidone nucleus is formed.[7–13]

We rationalized that a solvent effect should be operating in the competition between the formal aza-[3+3] versus aza-[3+2] cycloadditions, because the reactions shown in Fig. 1 with acyclic enaminones were performed in polar solvents, while Nagasaka employed benzene. In this way, we reevaluated the reaction of **12a** with **1** in polar solvents. After some experimentation, we discovered that in CH_2Cl_2 and CH_3CN the same indolizidinone **13** was obtained in yields slightly better than in benzene as solvent (Table 1, entries 2 and 4). Curiously, using $CHCl_3$ as solvent, indolizidinone **13** was obtained together with the isomeric pyrrolizidinone **14** (entry 3), as well as when the reaction was carried out in CH_3CN at reflux (entry 5). Despite **14** being formed in low yield, this aza-[3+2] product was not previously observed in the aza-annulation described by Nagasaka.[15]

Our synthetic enrollment with bismuth salts as Lewis acids in organic synthesis[21] prompted us to use bismuth iodine in CH_3CN, which increased the amount of isolated aza[3+2] product **14** (entries 6 and 7), being this the best condition to the one-pot synthesis of the pyrrolizidinone **14**. However, the formal aza[3+3] product **13** was always formed as the major or exclusive compound in all conditions herein studied with five-membered enaminone **12a** and maleic anhydride. This was also the result in the reaction of chiral cyclic enaminone **12b**, which allowed isolation of inseparable mixture of epimeric indolizidinones **15a**,**b** in good yield, Scheme 1.

The structure of pyrrolizidinone **14** was elucidated based on the spectral analysis. Moreover, during the synthetic methodology development, a single crystal of **14** was obtained and its solid state structure was unambiguously assigned to gain insight into conformational bias and intramolecular and intermolecular interactions, Fig. 2.

Distinction between indolizidinone **13** and isomeric pyrrolizidinone **14** could be easily done through analyses of their ^{1}H NMR data of the moiety corresponding to the atoms from maleic anhydride, Fig. 3. Thus, the endocyclic conformationally restricted $COCH_2CHCO_2H$ spin system of **13** appears as an AMX system, while the equivalent moiety $COCHCH_2CO_2H$ of **14** is an ABX one. Besides, the multiplicities of CH_2 in **13** are two double doublet (2.61 and 2.87 ppm), and the methynic hydrogen is a large double doublet (3.78 ppm). In the pyrrolizidinone **14**, the free rotation of exocyclic α methylene results in almost the same ^3J value to the coupling constant of the two hydrogen of CH_2 with vicinal CH, and then each hydrogen CH_2 of **14** appears as double doublets (3.00 and

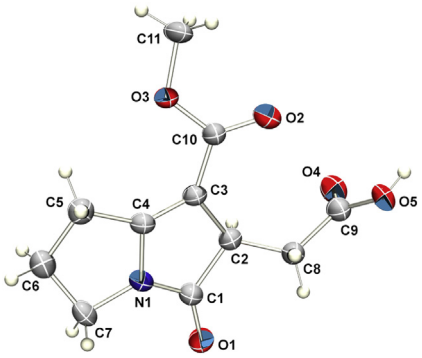


Fig. 2. Ortep[27] representation of pyrrolizidinone **14**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radius.

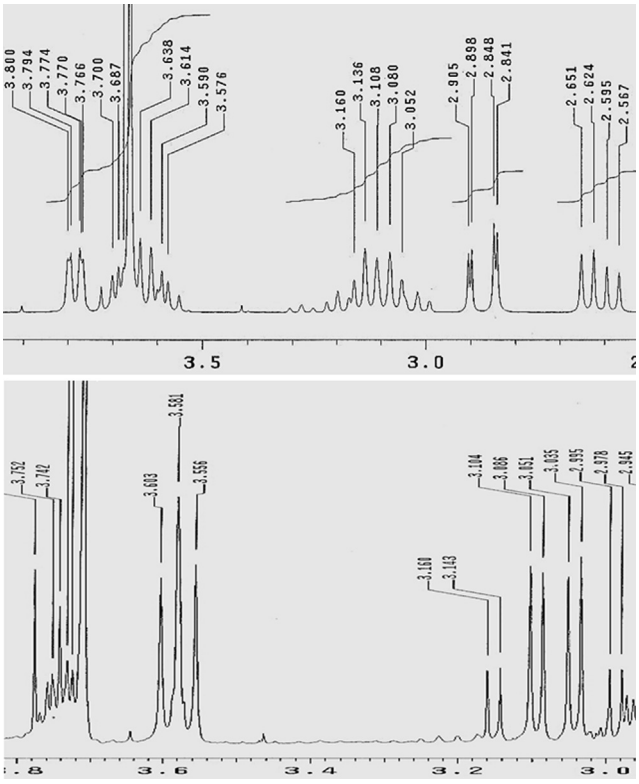


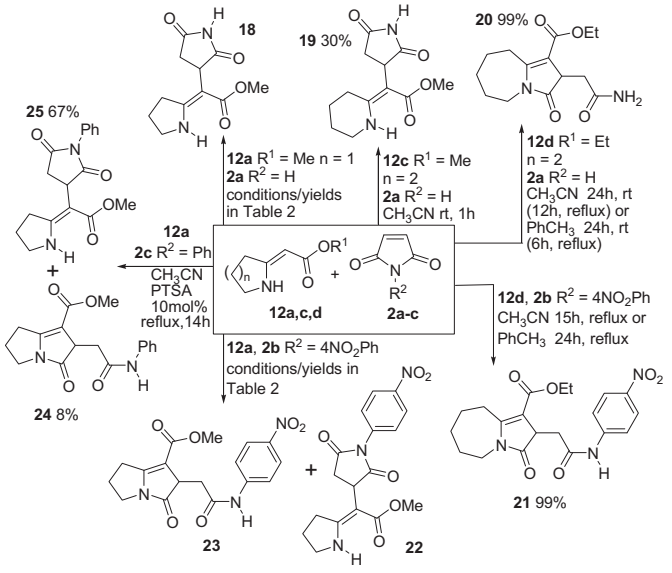
Fig. 3. Partial ^{1}H NMR spectra of **13** (top) and **14** (bottom) shown the spin systems $COCH_2CHCO_2H$ and $COCHCH_2CO_2H$, respectively.

3.12 ppm), and the methynic hydrogen is an apparent triplet (3.58 ppm), Fig. 3.[26]

To understand the scope of the aza-annulation, reactions of **1** with six and seven-membered enaminones **12c**,**d** were investigated. CH_3CN was selected as solvent due to the good solubility of the reagents, and because afforded clean reaction with enaminone **12a** at room temperature. In this condition, only formal aza-[3+2] cycloaddition products indolizidinone **16** and pyrroloazepinone **17** were generated in excellent yield from **12c** and **12d**, respectively, Scheme 1. These facts are in contrast with the behavior of five-membered enaminones **12a**,**b** in the reaction with maleic anhydride, which form exclusively indolizidinones **13** and **15a**,**b** by aza-[3+3] cycloaddition.[28]

It should be pointed out that obtained indolizidinones **13** and **16** are complementary in terms of ring substitution, because in the aza [3+3] product **13** the functionalizations are at the new formed six-membered ring, while they are located at the five-membered ring of the aza[3+2] product **16**. Moreover, the results of present study indicated that the formal aza-[3+3] cycloaddition of maleic anhydride, in useful yields, is exclusive to five-membered heterocyclic enaminones, while the one-pot synthesis of 1-azabicyclo[4.3.0] nonane and 1-azabicyclo[5.3.0]decane was accessed by the formal aza-[3+2] cycloaddition. However, this approach is not practical to the synthesis of 1-azabicyclo[3.3.0]octane. To overcome this limitation, we turned our attention to maleimides as alternative biselectrophile, because there is one example of one-step formal aza-[3+2] cycloaddition with enaminone in good yield.[13]

Initially, the search for selective formation of aza-[3+2] product with heterocyclic enaminone **12a** prompted us to try the reaction using maleimide **2a** in polar and apolar solvents, Scheme 2. However, only Michael adduct **18** was formed in excellent yield, Table 2 (entries 1–4). Contrary to the clean reaction with **12a**, reaction of **2a** with enaminone **12c** formed a complex mixture, and after purification Michael adduct **19** was isolated in low yield. To our delight, enaminone **12d** afforded aza-[3+2] products **20** and **21** in quantitative yields from **2a** and *N*-(4-NO_2Ph)maleimide **2b**, respectively, in both polar/apolar investigated solvents, Scheme 2. Stimulated by this results, the best conditions achieved for **12d** was extended to enaminone **12a** and maleimide **2b**, but here again only Michael adduct **22** was formed, Table 2 (entries 5–7).



Scheme 2. Reactions of cyclic enaminones with maleimides.

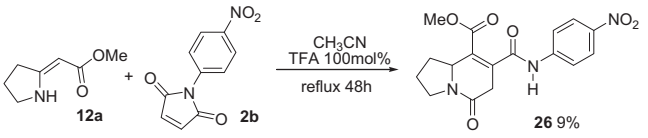
Table 2
Reaction conditions to the reaction of enaminone **12a** and maleimides **2a**,**b**

Entry	Maleimide	Conditions	Time	Yield (%)		
			(h)	**18**	**22**	**23**
1	**2a**	CH_3CN rt	72	96		
2	**2a**	CH_3CN reflux	12	94		
3	**2a**	PhH reflux	48	78		
4	**2a**	$PhCH_3$ reflux	24	99		
5	**2b**	CH_3CN reflux	12.5		95	
6	**2b**	PhH reflux	28		72	
7	**2b**	$PhCH_3$ reflux	21		81	
8	**2b**	CH_3CN rt TFA 100 mol %	240	Complex mixture		
9	**2b**	CH_3CN rt PTSA 20 mol %	216			28
10	**2b**	$CHCl_3$ reflux TFA 100 mol %	70			38
11	**2b**	$PhCH_3$ 60 °C TFA 100 mol %	66			70
12	**2b**	CH_3CN reflux PTSA 20 mol %	14		8	72

Evaluating all results herein obtained in the reactions of five-membered enaminone **12a** with anhydride **1** (Table 1, entries 1–5) and maleimides **2a**,**b** (Table 2, entries 5–7) revealed that formal aza-[3+3] cycloaddition and Michael reaction are the predominate reactions under thermal conditions, and acid catalysis seems to be necessary for the formal aza-[3+2] cycloaddition can compete with these reactions (Table 1, entries 6 and 7). With this work hypothesis in mind, we decided to try the reaction of **12a** with **2b** under acid conditions. Thus, after some initial experimentation, the use of acid conditions showed to be adequate, because in almost all reactions pyrrolizidinone **23** could be finally isolated (Table 2, entries 8–12). When the solvent was acetonitrile at room temperature, a very slow reaction took place using TFA 100 mol % or PTSA 20 mol % (entries 8 and 9). In addition, yield increased and reaction time decreased in the reaction carried out in $CHCl_3$ or toluene under reflux in the presence of 100 mol % TFA (entries 10 and 11). However, the reaction time was still long with excess acid.

Formation of aza-[3+2] product **23** could be satisfactorily accomplished in good yield as major compound, and in reasonable reaction time, using catalytic amount of PTSA in CH_3CN, Table 2 (entry 12). We extended this best condition to *N*-phenylmaleimide **2c**, and Michael adduct **25** was the major product instead of aza-[3+2] compound **24**, Scheme 2.[29] These results indicate that the combination of the strong electron withdrawing nitro group at *N*-aryl ring of maleimide, and PTSA catalysis appears to be crucial to the successful formation of pyrrolizidinone nucleus through formal aza-[3+2] cycloaddition reaction of heterocyclic five-membered enaminone and *N*-arylmaleimide.

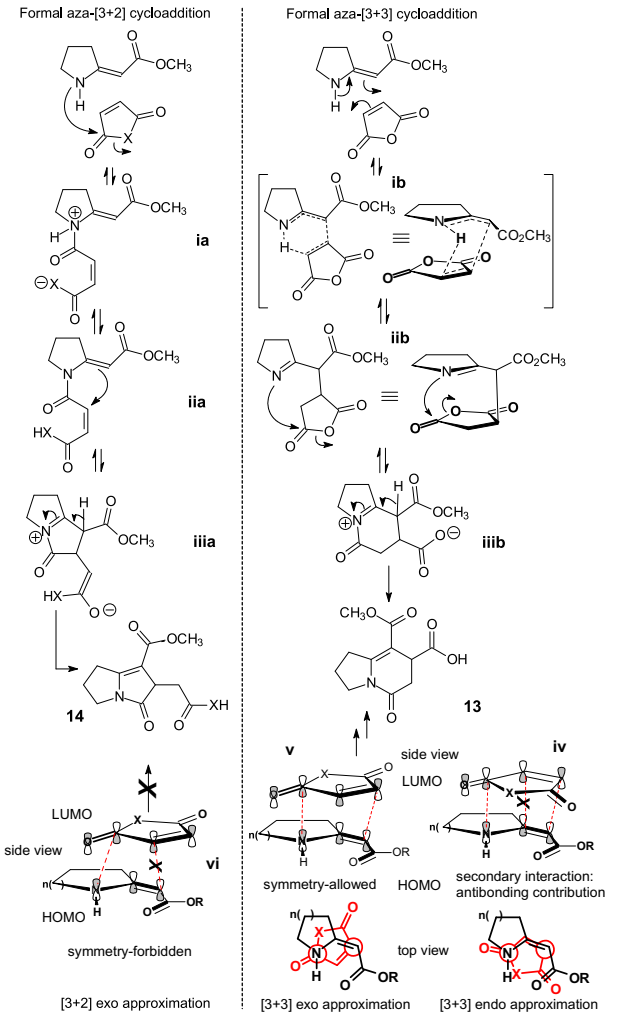
Contrary to the general trend, reaction of **12a** with maleimide **2b** furnished a complex mixture when TFA 100 mol % in CH_3CN was used (Table 2, entry 8), but a small amount of indolizidinone **26** could be isolated, Scheme 3. Interestingly, this is the unique example to date of one-pot indolizidinone formation from reaction of maleimide with **12a** where double bond migration was observed.



Scheme 3. Aza-[3+3] reactions of cyclic enaminone with maleimide.

Mechanistic considerations were formulated to the formation of pyrrolizidinones, pyrroloazepinones, and indolizidinones herein synthesized, and two postulated reaction pathways are exemplified in Scheme 4 to the reaction of five-membered enaminone and maleic anhydride.[30] The formal aza-[3+2] cycloaddition can be rationalized as an ionic stepwise process whereby the key step is initiated by attachment of the nitrogen of the enaminone to the carbonyl carbon of **1** via a hard-hard interaction, probably by a charge controlled reaction. Adduct **ia** is thus formed, which in sequence forms maleamic acid derivative **iia**, Scheme 4. This late suffers a 5-*exo*-*trig* cyclization via a Michael reaction forming enolate **iiia**, which gives **14** after proton shift. Meanwhile, the formal aza-[3+3] cycloaddition pathway to indolizidinone formation may be rationalized assuming a concerted aza-ene reaction through transition state **ib**, corresponding to soft–soft interaction under orbital controlled reaction, probably via a compact approximation,[31] which gives intermediate **iib**. In sequence, intramolecular N-acylation of **iib** occurs by the nitrogen attack to the nearest carbonyl group, forming enolate **iiib**. Here again, isomerization to the enamide affords bicycle **13**.

The compact transition state for the [3+3] aza-annulation should explain why enaminones **12c**,**d** did not react by this reaction



Scheme 4. Mechanistic proposals to [3+3] and [3+2] aza-annulations (X=O/NAr): (top) stepwise pathways; (bottom) approximation rationalization.

mode with **1**.[31] The presence of more flexible six and seven-membered rings in **12c**,**d**, as compared to **12a**, can be responsible for a sterically hindered environment of transition state alike **ib**, avoiding such approximation for these cyclic enaminones, and thus driving the initial attack of the nitrogen to the carbonyl carbon of **1**, according to aza-[3+2] pathway in Scheme 4.

Frontier orbital analysis can also explain the different behavior of the five-membered enaminones **12a**,**b** and the six- and seven-membered-ring enaminones **12c**,**d** on reaction with maleic anhydride (Scheme 4, right column). The [3+3] approach of the reagents can take place via an *endo* **iv** or *exo* **v** mode. The signs of the coefficients in the HOMO of enaminones[32] **12a**–**d** are favorable to bonding interaction at carbon 2 and 4 of maleic anhydride with N1 and C3 of **12a**–**d**. However, in the [3+3] *endo* approach **iv**, a secondary antibonding interaction occurs, leading to a transition state, which should be more energetic than *exo* approach **v**. The favored *exo* mode **v** is very sensitive to the bulk and planarity of the reagents. Thus, replacement of the more planar five-membered enaminones **12a**,**b** by the more flexible six and seven-membered rings of **12c**,**d** results in a more hindered environment, that is, unfavorable to *exo* [3+3] approximation, and thus the [3+2] reaction pathway is followed. Similar *endo*/*exo* mode to the [3+2] reaction is not favored due symmetry-forbidden orbital interaction depicted in *exo* **vi** (Scheme 4, left column).

When maleimides (where X=NH or NAr) are used instead of maleic anhydride, the soft-soft interactions are boosted. Therefore,

both the five- and six-membered enaminones **12a** and **12c**, respectively, give **iib** products (compounds **18** and **19**). However, the seven-membered cyclic enaminone **12d** gives predominantly the [3+2] product **20**. The [3+2] way is also favored when the Ar group presents strong electron-withdrawing substituents, since in this case hard–hard interactions are increased. The addition of acid also favors the hard–hard interactions, because the carbonyl protonation of the maleimide **2b** makes it a harder electrophile.[33]

3. Conclusion

This study shown the successful one-step skeletally diverse synthesis of alkaloid-like pyrrolizidinones, indolizidinones, and pyrroloazepinones based on simple domino reactions of heterocyclic enaminones[34] with maleic anhydride or *N*-aryl-maleimides.

To access selectively such heterocycles, the reaction course can be convenient controlled, switching between aza-[3+3] and aza-[3+2] modes of formal cycloaddition, being modulated by the nature of enaminone, electrophile employed, and acid catalysis. Thus, for the synthesis of pyrroloazepinones (**17**, **20**, **21**), the seven-membered enaminone and maleic anhydride or maleimides were efficient, via the [3+2] mode of cyclization. To access indolizidinones (**13**, **15**, **16**) in good yield, five or six-membered enaminones are the choice, and both [3+2] and [3+3] modes were viable exclusively with maleic anhydride. At last but not least, pyrrolizidinone **23** could be selectively synthesized in good yield through the [3+2] mode only with five-membered enaminone and *N*-(4-NO_2Ph)maleimide under catalysis by PTSA. In this way, the present contribution sheds new light on the chameleonic behavior of heterocyclic enaminones in the aza-annulations with anhydride maleic and *N*-arylmaleimides, as well as increases the synthetic possibilities of the formal aza-cycloaddition reactions of such enaminones.[34]

4. Experimental section

4.1. General

Melting points were determined on a Microquímica MQAPF 301 hot plate apparatus and are uncorrected. Infrared spectra of solid samples were recorded as KBr discs, and oleo samples as films, on an FT-IR BOMEM MB100 instrument. NMR spectra were obtained for ^{1}H at 250 MHz, 300 MHz or 500 MHz, and for ^{13}C at 62.5 MHz, 75 MHz or 125 MHz using Varian Gemini or INOVA and Brucker Avance spectrometers. Chemical shifts are reported in parts per million units downfield from reference (internal TMS or residual undeuterated solvent). Elemental analyses were performed on a Flash 2000 Thermo Scientific instrument at Instituto de Química/UFG. The high resolution mass spectra were recorded using a Q-TOF equipment (Waters, UK) at Instituto de Química/Unicamp. Maleimides **2b**,**c**[35] and enaminones **12a**–**d**[25] were prepared according to known procedures.

4.2. General synthetic procedure for the indolizidinones 13, 15–16, pyrrolizidinone 14, and pyrrolo[1,2-*a*]azepinone 17

A solution of heterocyclic enaminone **12a**–**d** (1.0 mmol) and anhydride maleic **1** (1.0 mmol) in the solvent (5.0 mL) and time indicated in each case, was magnetic stirring at room temperature. After this, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel.

*4.2.1. Indolizidinone **13**.* Dichloromethane, 0.5 h. Purified by silica gel column chromatography eluent hexane/ethyl acetate 4:1 (v/v), brown solid, 85% yield, mp 140.7–142.0 °C. ^{1}H NMR ($CDCl_3$) δ 1.92 (qt, *J* 7.2 Hz, 2H), 2.61 (dd, *J* 17.1 and *J* 8.4 Hz, 1H), 2.87 (dd, *J* 17.1 and 2.1 Hz, 1H), 3.00–3.22 (m, 2H), 3.55–3.72 (m, 2H), 3.66 (s, 3H), 3.78 (dd, *J* 8.4 and 2.1 Hz, 1H), 9.60–9.90 (sl, 1H). ^{13}C NMR ($CDCl_3$) δ 20.91 (CH_2), 32.10 (CH_2), 33.08 (CH_2), 38.19 (CH_2), 46.19 (CH_3), 51.68 (CH), 98.03 (C), 155.55 (C), 167.19 (C), 167.40 (C), 176.45 (C). IR (cm^{-1}): 1739, 1685, 1635, 1380. Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23%; H, 5.48%; N, 5.86%. Found: 55.80%; H, 5.27%; N, 5.80%.

*4.2.2. Pyrrolizidinone **14** and indolizidinone **13**.* Acetonitrile, 1 mmol of BiI_3, 1 h, 36% and 50% yield, respectively. Purified by silica gel column chromatography eluent hexane/ethyl acetate/methanol 1:1:0.2 (v/v). Compound **14**: yellow solid, 36% yields, mp 156.0–157.8 °C. ^{1}H NMR ($CDCl_3$) δ 2.38 (qt, *J* 7.0 Hz, 2H), 2.91 (dd, *J* 7.0 and *J* 3.0 Hz, 1H), 2.95 (dd, *J* 7.0 and 3.0 Hz, 1H), 3.01 (dd, *J* 17.1 and 5 Hz, 1H), 3.12 (dd, *J* 17.1 and 5.2 Hz, 1H), 3.58 (t, *J* 7.0 Hz, 2H), 3.71 (s, 3H), 3.72–3.76 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 25.76 (CH_2), 26.20 (CH_2), 33.19 (CH_2), 41.42 (CH_2), 48.17 (CH_3), 51.00 (CH), 101.12 (C), 162.67 (C), 164.05 (C), 175.16 (C), 175.77 (C). IR (cm^{-1}): 1739, 1703, 1668, 1436, 1375. Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23%; H, 5.48%; N, 5.86%. Found: 54.99%; H, 5.15%; N, 5.62%.

*4.2.3. Indolizidinones **15a**,**b**.* Dichloromethane, 24 h, 73% yield, brown oil (two diastereomers). Purified by silica gel column chromatography eluent chloroform/ethanol 7:3 (v/v). Compound **15a**: ^{1}H NMR ($CDCl_3$) δ 1.85–2,20 (2H), 1.96 (s, 3H), 2.65 (dd, *J* 16.8 and 7.8 Hz, 1H), 2.93 (dd, *J* 16.8 and 2.7 Hz, 1H), 3.29 (dd, *J* 9.6 and 2.7 Hz, 1H) 3.70–3.90 (1H), 3.77 (s, 3H), 4.02 (dd, *J* 11.1 and 3.6 Hz, 1H), 4.31–4.38 (1H), 4.44 (d, *J* 4.5 Hz, 1H), 4.54–4.62 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 20.55 (CH_3), 24.10 (CH_2), 31.07 (CH_2), 33.04 (CH_2), 38.09 (CH_2), 51.68 (CH), 56.63 (CH_3), 63.10 (CH_2), 97.83 (C), 155.44 (C), 166.85 (C), 167.27 (C), 170.65 (C), 175.80 (C). Compound **15b**: ^{1}H NMR ($CDCl_3$) δ 1.85–2.20 (2H), 2.04 (s, 3H), 2.73 (dd, *J* 16.8 and 8.4 Hz, 1H), 2.98 (dd, *J* 16.8 and 3.0 Hz, 1H), 3.38 (dd, *J* 17.4 and 3.0 Hz, 1H) 3.70–3.90 (1H), 3.77 (s, 3H), 4.10 (dd, *J* 11.4 and 3.0 Hz, 1H), 4.31–4.38 (1H), 4.48 (d, *J* 4.2 Hz, 1H), 4.54–4.62 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 20.76 (CH_3), 24.76 (CH_2), 31.07 (CH_2), 33.77 (CH_2), 38.38 (CH_2), 51.78 (CH), 56.75 (CH_3), 64.27 (CH_2), 98.62 (C), 155.78 (C), 166.93 (C), 167.40 (C), 170.89 (C), 176.10 (C).

*4.2.4. Indolizidinone **16**.* Acetonitrile, 1 h. Purified by silica gel column chromatography eluent hexane/ethyl acetate 1:1 (v/v), yellow oil, 88% yields. ^{1}H NMR ($CDCl_3$) δ 1.65–1.88 (m, 4H), 2.84–3.15 (m, 2H), 3.39–3.50 (m, 2H), 3.52–3.63 (m, 2H), 3.71 (s, 3H), 9.40–9.80 (sl, 1H). ^{13}C NMR ($CDCl_3$) δ 19.22 (CH_2), 21.55 (CH_2), 24.65 (CH_2), 33.46 (CH_2), 40.13 (CH_2), 42.34 (CH_3), 50.65 (CH), 103.93 (C), 156.15 (C), 164.26 (C), 175.39 (C), 178.71 (C). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91%; H, 5.97%; N, 5.53%. Found: C, 57.23%; H, 6.11%; N, 5.65%.

*4.2.5. Pyrrolo[1,2-a]azepinones **17**.* Acetonitrile, 1 h. Purified by silica gel column chromatography hexane/ethyl acetate 1:1 (v/v), white solid, 99% yield, mp 153.2–154.7 °C. ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J* 7.0 Hz, 3H), 1.50–1.85 (m, 6H), 2.29–2.42 (m, H), 2.70–2.88 (m, 1H), 2.99 (dd, *J* 17.1 and 4.9 Hz, 1H), 3.19 (dd, *J* 17.1 and 4.9 Hz, 1H), 3.46 (dt, *J* 4.9 and 1.2 Hz, 1H), 3.49–3.60 (m, 1H), 3.82–3.92 (m, 1H), 4.09–4.27 (m, 2H), 10.02 (sl, 1H). ^{13}C NMR ($CDCl_3$) δ 13.91 (CH_3), 25.69 (CH_2), 26.21 (CH_2), 28.17 (CH_2), 30.11 (CH_2), 33.51 (CH_2), 40.63 (CH_2), 42.75 (CH), 59.45 (CH_2), 103.95 (C), 160.76 (C), 163.71 (C), 175.18 (C), 177.27 (C). IR (cm^{-1}): 3453, 1706, 1691, 1684. Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78%; H, 6.81%; N, 4.98%. Found: C, 59.71%; H, 6.65%; N, 5.22%.

4.3. General synthetic procedure for the pyrrolizidinones 23, 24, pyrrolo[1,2-*a*]azepinones 20, 21, succinimides 18, 19, 22, and 25

A solution of heterocyclic enaminone **12a**,**b**,**d** (1.0 mmol) and maleimide **2a**–**c** (1.0 mmol) in the solvent (5.0 mL), temperature

and time indicated in each case, was magnetic stirring. After this, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel when necessary.

4.3.1. Michael adduct ***18***. Toluene, reflux 24 h. The reaction mixture was concentrated and purification was not necessary, brown oil, 99% yield. ^{1}H NMR ($CDCl_3$) δ 1.89 (m, 2H), 2.32 (dd, *J* 17.7 and 5.4 Hz, 1H), 2.64 (t, *J* 7.5 Hz, 2H), 2.81 (dd, *J* 17.7 and 9.3 Hz, 1H), 8.22 (sl, 1H), 10.91 (sl, 1H). ^{13}C NMR (DMSO-d_6) δ 21.25 (CH_2), 31.59 (CH_2), 37.23 (CH_2), 41.98 (CH_2), 47.70 (CH_3), 50.06 (CH), 84.90 (C), 165.79 (C), 167.98 (C), 178.48 (C), 181.64 (C). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46%; H, 5.92%; N, 11.76%. Found: C, 55.78%; H, 6.32%; N, 11.28%.

4.3.2. Michael adduct ***19***. Acetonitrile, room temperature 8 h. Purified by silica gel column chromatography hexane/ethyl acetate 1:1 (v/v), brown oil, 30% yield. ^{1}H NMR ($CDCl_3$) δ 1.62–1.83 (m, 6H), 2.58 (dd, *J* 18.3 and 5.6 Hz, 1H), 2.87 (dd, *J* 18.3 and 8.8 Hz, 1H), 8.83 (sl, 1H), 9.82 (sl, 1H), the rest overlapping signals. ^{13}C NMR ($CDCl_3$) δ 19.73 (CH_2), 21.67 (CH_2), 26.24 (CH_2), 37.50 (CH_2), 39.87 (CH_2), 41.43 (CH), 50.21 (CH_3), 86.23 (C), 134.93 (C), 161.83 (C), 169.04 (C), 177.55 (C), 181.22 (C).

4.3.3. Pyrrolo[1,2-a]azepinones ***20***. Toluene, reflux 6 h. The reaction mixture was concentrated and purification was not necessary, yellow solid, 99% yield, mp 149–151 °C. ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J* 7.2 Hz, 3H), 1.62–1.82 (m, 6H), 2.80–3.06 (m, 1H), 2.88 (dd, *J* 15.3 and 6.3 Hz, 1H), 2.94 (dd, *J* 15.3 and 4.2 Hz, 1H), 3.12–3.25 (m, 1H), 3.56–3.68 (m, 1H), 3.76–3.88 (m, 1H), 4.12–4.25 (m, 2H), 5.37 (sl, 1H), 6.02 (sl, 1H). ^{13}C NMR ($CDCl_3$) δ 14.39 (CH_3), 26.19 (CH_2), 26.60 (CH_2), 28.62 (CH_2), 30.46 (CH_2), 35.44 (CH_2), 40.92 (CH_2), 43.65 (CH), 59.74 (CH_2), 104.46 (C), 160.62 (C), 164.16 (C), 172.06 (C), 177.98 (C). Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99%; H, 7.19%; N, 9.99%. Found: C, 60.41; H, 8.31%; N, 9.61%.

4.3.4. Pyrrolo[1,2-a]azepinones ***21***. Acetonitrile, reflux 15 h. The reaction mixture was concentrated and purification was not necessary, yellow solid, 99% yield, mp 212.8–214 °C. ^{1}H NMR (DMSO-d_6) δ 1.10–1.20 (m, 3H), 1.60–1.80 (m, 6H), 2.07 (t, *J* 0.6 Hz, 1H), 2.93 (dd, *J* 15.9 and 5.1 Hz, 1H), 3.06 (dd, *J* 15.9 and 5.1 Hz, 1H), 3.54 (t, *J* 4.5 Hz, 2H), 4.05 (m, 2H), 7.82 (d, *J* 9 Hz, 2H), 8.30 (d, *J* 9 Hz, 2H), 10.6 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 10.13 (CH_3), 21.22 (CH_2), 22.17 (CH_2), 24.17 (CH_2), 25.61 (CH_2), 32.34 (CH_2), 34.66 (CH_2), 38.72 (CH), 55.02 (CH_2), 99.55 (C), 114.55 (C), 120.95 (C), 138.02 (CH), 141.16 (CH), 156.57 (C), 159.48 (C), 165.32 (C), 172.79 (C), 180.40 (C). Anal. Calcd for $C_{20}H_{23}N_3O_6$: C, 59.84%; H, 5.78%; N, 10.47%. Found: C, 60.04%; H, 6.02%; N, 10.10%.

4.3.5. Michael adduct ***22***. Acetonitrile, reflux 12.5 h. Recrystallized in ethanol, white solid, 95% yield, mp 171.3–173.5 °C. ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 2H), 2.55 (dd, *J* 8.1 and 2.7 Hz, 1H), 2.74 (t, *J* 8.1 Hz, 2H), 3.15 (dd, *J* 18 and 9.6 Hz, 1H), 3.30 (s, 3H), 3.47–3.53 (overlapping signals, 2H), 3.78–3.84 (sl, 1H), 7.60 (d, *J* 8.2 Hz, 2H), 8.28 (sl, 1H), 8.40 (d, *J* 8.2 Hz, 2H). IR (cm^{-1}): 3360, 1709, 1662, 1346. Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82%; H, 4.77%; N, 11.69%. Found: C, 56.88%; H, 4.77%; N, 11.72%.

4.3.6. Pyrrolizidinone ***23***. Acetonitrile and 20 mol % of PSTA, reflux 72 h. Reaction mixture was cooled to 0 °C and the formed solid was washed with cold acetonitrile, yellow solid, 74% yield, mp 204.7–207.8 °C. ^{1}H NMR (DMSO-d_6) δ 2.22–2.37 (m, 2H), 2.85–2.89 (m, 2H), 2.94 (dd, *J* 5.1 and 16.1 Hz, 1H), 3.08 (dd, *J* 5.4 and 16.1 Hz, 1H), 3.47–3.52 (m, 2H), 3.57 (m, 1H), 3.77–3.85 (m, 1H), 7.78 (d, *J* 9.2 Hz, 2H), 8.20 (d, *J* 9.2 Hz, 2H), 10.57 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 25.58 (CH_2), 25.78 (CH_2), 35.68 (CH_2), 41.08 (CH_2), 47.80 (CH_3), 50.53 (CH), 100.06 (C), 118.62 (CH), 124.96 (CH), 142.03 (C), 145.15 (C), 162.93 (C), 163.43 (C), 169.40 (C), 174.62 (C). IR (cm^{-1}): 3215, 3083, 1683, 1562, 1319, 1089, 854, 752, 607. HRMS (ESI) calcd for $C_{17}H_{18}N_3O_6$: 360.1196 $[M+H]^+$; Found: 360.1133 $[M+H]^+$.

4.3.7. Pyrrolizidinone ***24*** *and Michael adduct* ***25***. Acetonitrile, reflux 14 h. Purified by silica gel column chromatography eluent hexane/ethyl acetate 3:2 to 1:4 gradient (v/v). **24**: white solid, 8% yield. ^{1}H NMR (DMSO-d_6) δ 2.25–2.36 (m, 2H), 2.81–2.91 (m, 3H), 3.01 (dd, *J* 5.4 and *J* 15.9 Hz, 1H), 3.45–3.52 (m, 2H), 3.58 (s, 3H), 3.74–3.80 (m, 1H), 7.00 (t, *J* 7.3 Hz, 1H), 7.27 (t, *J* 7.8 Hz, 2H), 7.52 (d, *J* 7.7 Hz, 2H), 9.90 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.13 (CH_2), 26.37 (CH_2), 36.79 (CH_2), 41.69 (CH_2), 49.24 (CH_3), 51.25 (CH), 101.40 (C), 120.10 (CH), 124.32 (C), 129.12 (CH), 138.13 (C), 162.82 (C), 164.57 (C), 168.35 (C), 175.91 (C). IR (cm^{-1}): 3464, 3448, 3317, 1693, 1678, 1600, 1539, 1377, 1242, 1084, 760, 698. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_4$: 315.1345$[M+H]^+$; Found: 315.1368 $[M+H]^+$.

Compound **25**: Pale yellow solid, 67% yield. ^{1}H NMR ($CDCl_3$) δ 1.99–2.17 (m, 2H), 2.63–2.94 (m, 3H), 3.07 (dd, *J* 9.7 and 18.1 Hz, 1H), 3.58–3.63 (m, 3H), 3.67 (s, 3H), 7.28 (d, *J* 7.8 Hz, 2H), 7.35–7.51 (m, 3H), 8.43 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 21.89 (CH_2), 31.79 (CH_2), 36.75 (CH_2), 41.06 (CH_2), 47.87 (CH_3), 50.92 (CH), 85.92 (C), 126.78 (CH), 128.60 (C), 129.36 (CH), 132.84(C), 168.95 (C), 176.38 (C), 179.22 (C). IR (cm^{-1}): 3464, 3367, 2947, 2850, 1709, 1659, 1593, 1385, 1184, 1057, 1033, 779, 683, 613, 536. HRMS (ESI) calcd for $C_{17}H_{19}N_2O_4$: 315.1345$[M+H]^+$; Found: 315.1379 $[M+H]^+$.

4.3.8. Indolizidinone ***26***. Pale yellow solid, 9% yield. ^{1}H NMR (DMSO-d_6) δ 2.13–2.31 (m, 2H), 2.71–2.82 (m, 2H), 2.98 (d, *J* 17.0 Hz, 1H), 3.23–3.28 (m, 1H), 3.43–3.47 (m, 1H), 3.53 (s, 3H), 3.92 (d, *J* 17.0 Hz, 1H), 7.74 (d, *J* 9.5 Hz, 2H), 8.17 (d, *J* 9.5 Hz, 2H), 10.73 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 25.9 (CH_2), 26.2 (CH_2), 35.3 (CH_2), 50.8 (CH), 59.9 (CH_3), 101.7 (C), 119.1 (C), 125.4 (C), 142.4 (CH), 145.6 (CH), 163.5 (C), 164.5 (C), 169.7 (C), 174.6(C).

4.4. X-ray analysis

A single-crystal of **14** suitable for data collection was mounted on a Bruker Kappa Apex II Duo diffractometer,[36] using Mo Kα radiation from an IμS micro source device, monochromatized using multi-layer mirror optics. Data collection has been carried out at room temperature by ω/φ scans. Cell refinement and data reduction was performed with Saint,[36] and the structure solution was obtained by Direct Methods using ShelxS97.[37] Non hydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms were refined isotropic with riding constraints to their parent atoms using ShelxL97.[37] $C_{22}H_{21}N_1O_3$, T=293(2) K, λ=0.71073 Å, μ=0.11 mm^{-1}, crystal size 0.27×0.17×0.09 mm, monoclinic, $P2_1/n$, a=7.6761(4) Å, b=10.0072(5) Å, c=14.5525(8) Å, β=90.180(3)°, volume 1117.86(10) Å^3, Z=4, D_c=1.421 Mg/m^3, θ range of data collection 2.47–25.73°, $-9\leq h\leq 9$, $-11\leq k\leq 12$, $-17\leq l\leq 17$, reflections collected 13,077, independent 2137, R(int)= 0.028, refinement using Full-matrix least-squares on F^2, 1469 data points, 293 parameters, 566 restraints (whole molecule disorder 0.54/046), GooF 1.101, $R1$=0.081, $wR2$=0.228 [$I>2\sigma(I)$], extinction coef. 0.004(2), the largest diff. peak and hole are 0.234 and −0.365 e Å^{-3}. The compound crystallizes in a general position of the unit cell, with static disorder on the whole molecule featured by the racemic counterparts, which occupations were refined to 0.542(5) and 0.458(5). In the crystal packing the molecules form intermolecular hydrogen bonds of type O5–H5···O1, with donor acceptor distance of 2.545(11) Å, DHA angle of 158.2°, the other disorder component presents this H-bond geometry 2.553(14) Å DHA angle 163.1°. This connects molecules related by the screw axis and builds an infinity linear chain though [010]. These chains are loosely stacked parallel to the (100) crystal plane.

CCDC 958810 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

The authors gratefully acknowledge the financial support of Conselho Nacional de Desenvolvimento Científico e Tecnológico—CNPq, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—CAPES, and Fundação de Amparo à Pesquisa do Estado da Bahia—FAPESB. We also thank FAPESB for student fellowship J.T.M.C. (PIBIC), CNPq for fellowship to A.O.S. and research fellowship to S.C., and Professor Mauricio Victor for discussion and comments.

Supplementary data

IR, ^{1}H NMR, and ^{13}C NMR spectra for **13**–**25**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.10.071.

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