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The synthesis of 2-ketopiperazine acetic acid esters and amides from ethylenediamines with maleates and maleimides

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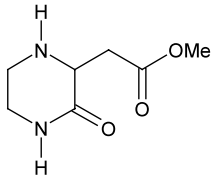
Abstract—The reaction of substituted ethylenediamines with various fumarates, maleates, and maleimides to form substituted ketopiperazine acetic acid esters and amides was investigated. This method affords a straightforward, high yield approach to a variety of potential peptidomimetics and can yield surprising results with regard to regio- and stereoselectivity.

The 2-oxopiperazine-3-acetic acid methyl ester, **1**, is an excellent example of an easily diversified template for combinatorial chemistry applications as a peptidomimetic in medicinal chemistry.[1] Although a number of new synthetic approaches to this class of molecules have recently appeared,[2] none have involved the simple addition of ethylenediamines to dialkyl maleates.[3] We wish to report here the results of this synthetic method and our investigations on the effect of varying substitution in the ethylenediamine (EDA) as well as the dimethyl maleate or dimethyl fumarate on the ketopiperazine product.



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Addition of *N*-methyl EDA to dimethyl maleate or dimethyl fumarate showed no regioselectivity, affording a 1:1 mixture of ketopiperazines (Fig. 1, Table 1, entry 1); however, addition of *N*-ethyl EDA afforded a useful level (10:1) of regioselectivity (entry 2). Substitution with bulkier groups, e.g. *N*-benzyl EDA or *N*-4-picolinyl EDA, gave an increase in regioselectivity to 20:1 (entries 4, 5). These examples lead to the conclusion that the least substituted nitrogen of the diamine preferably adds first in 1,4 fashion with subsequent amide formation by the tethered secondary amine. Methyl and *gem*-dimethyl EDA chain substitution did not alter this trend (entries 6, 7) nor was any stereo induction during heterocycle formation noted (entry 6).[3c] It is not known whether the observed 1:1 ratio of diastereomers of entry 6 arises from protonation of the intermediate enolate or epimerization after ring closure. Reaction of *N*-methyl-*N*′-ethyl EDA provides the expected *N*-ethylamide as the major isomer in a synthetically useful ratio of 14:1 as determined from ^{13}C NMR analysis (entry 3). The same 14:1 ratio was obtained starting with either dimethyl maleate or dimethyl fumarate. These results support the premise that the least hindered nitrogen of the diamine adds in Michael fashion to the maleate or fumarate. When the substituent on one diamine nitrogen becomes sufficiently sterically bulky or non-nucleophilic, 1,4-addition to the double bond by the least hindered nitrogen takes place, but subsequent ring closure only occurs under more forcing conditions (entries 8, 9, 10) if at all. Similar results were obtained in a variety of solvents used to effect ketopiperazine formation, e.g. diethyl ether, *p*-dioxane, toluene and alcohols.[3]

We next investigated the reaction of substituted EDAs with dimethyl citraconate and dimethyl phenylmaleate (Fig. 2, Table 2).[5] To our amazement, the reaction of EDA with dimethyl citraconate provided a single ketopiperazine, **5**, containing a *quaternary* carbon (Table 2, entry 1).[3b] This result was based on analysis of the ^{13}C NMR DEPT which showed a quaternary

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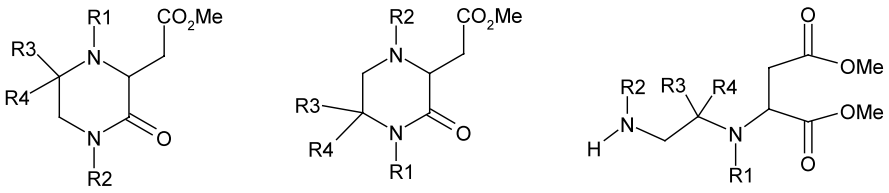

Figure 1. Products of the reaction of ethylene diamines with dimethyl maleates and fumarates.

Table 1. Reaction of ethylenediamines with dimethyl maleate and fumarates[a]

Entry	R1	R2	R3	R4	Yield (%)	**2**	**3**	**4**
1	H	Me	H	H	91	50	50	0
2	H	Et	H	H	95	91	9	0
3	Me	Et	H	H	88	93	7	0
4	H	Bn	H	H	86	96	4	0
5	H	4-Pi	H	H	87	96	4	0
6	H	H	Me	H	75	–	100	0
7	H	H	Me	Me	77	–	100	0
8	H	*i*-Bu	H	H	82	–	0	100[b]
9	H	Ph	Me	Me	78	–	0	100[c]
10	H	Ph	H	H	83	–	0	100[d]

[a] Ph = Phenyl. Bn = Benzyl. Me = Methyl. Et = Ethyl. *i*-Bu = *iso* butyl. Pi = Picolinyl. All reactions carried out in MeOH at 25°C for 24 h unless noted. All compounds were fully characterized by high field ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and FTIR. Entries 1–6 were characterized analytically as mixtures, and the ratios determined by ^{1}H NMR and ^{13}C NMR. Entry 6 was characterized as a 1:1 mixture of diastereomers.

[b] Only 1,4-addition was noted at room temperature with ca. 50% cyclization occurring after heating at 65°C for 24 h.

[c] Only 1,4-addition was noted room temperature with ca. 30% cyclization occurring after heating at 65°C for 24 h.

[d] Only 1,4 addition was noted at room temperature with no cyclization to ketopiperazine even after prolonged heating at 65°C.

carbon at 57.7 ppm and by ^{1}H NMR which showed a methyl singlet at 1.4 ppm and a clean AB pattern for the methylene alpha to the ester at 2.50 and 3.05 ppm. This indicates that the EDA added in a 1,4 fashion first at the more substituted end of the citraconate double bond with subsequent amide formation by the tethered amine. Reaction with *N*-methyl or *N*-ethyl EDA also gave products resulting from attack of the primary nitrogen of the diamine at the more hindered end of the citraconate double bond affording regiospecifically the *N*-alkyl amides (entries 2, 3). Methyl or *gem*-dimethyl groups on the diamine backbone do not affect the regiospecificity, and, in the case of the monomethyl diamine, gave a 1:1 mix of diastereomers (entries 4, 5). This was easily determined by ^{1}H NMR integration of the methyl doublets and the quaternary methyl protons (R5). Entry 3, as in entry 6 of Table 1, showed no stereo induction during heterocycle formation. Use of dimethyl phenylmaleate as the electrophile with EDA afforded a different result where the amine added preferentially 1,4 at the least substituted end of the phenylmaleate double bond providing regiospecifically a 1.5:1 mixture of diastereomers (entry 6). *N*-Methyl EDA reacted with dimethyl phenylmaleate to provide a 20:1 mixture of regioisomers each as a 2:1 diastereomeric pair of ketopiperazines (entry 7). The least hindered end of the EDA prefers to add first followed by amide ring closure. Again it is not known whether the observed diastereomers arise from protonation of the intermediate enolate of the initial 1,4-addition or epimerization after ring closure. With disubstituted dimethyl or diphenyl maleates, ethylenediamine gave no reaction even after heating at 65°C for 24 hours (entries 8, 9).

We then extended our investigation to the reaction of EDAs with maleimides (Fig. 3, Table 3).[6] Though this reaction has a precedent,[3b] its synthetic potential has not been widely explored. Reaction of *N*-methyl EDA with *N*-phenyl and *N*-H maleimide resulted in a rapid, clean conversion to another unexpected, regiospecific product (entries 1, 2). Surprisingly, the more substituted end of the diamine was found to add initially to the maleimide double bond followed by ring formation by the tethered primary amine. This is in contrast to the additions to maleates and fumarates (Table 1, entries 2, 4, 5) where the unsubstituted end of the EDA added initially to the double bond. The structural assignments

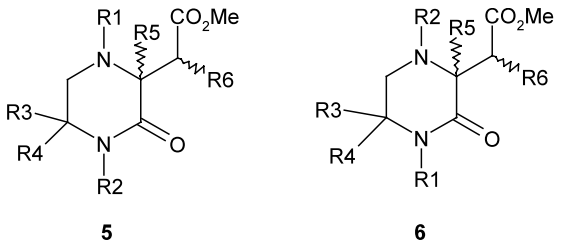

Figure 2. Products of the reaction of ethylene diamines with dimethyl citraconates and phenyl maleates.

Table 2. Reaction of ethylenediamines with dimethyl citraconates and phenyl maleates[a]

Entry	R1	R2	R3	R4	R5	R6	Yield (%)	**5**	**6**
1	H	H	H	H	Me	H	65	100	–
2	H	Me	H	H	Me	H	63	100	0
3	H	Et	H	H	Me	H	68	100	0
4	H	H	H	Me	Me	H	68	100	0
5	H	H	Me	Me	Me	H	91	100	0
6	H	H	H	H	H	Ph	75	100	0
7	H	Me	H	H	H	Ph	85	95	5
8	H	H	H	H	Me	Me	[b]	–	–
9	H	H	H	H	Ph	Ph	[b]	–	–

[a] Ph = Phenyl. Me = Methyl. Et = Ethyl. All reactions carried out in MeOH at 25°C for 24 h unless noted. All compounds and mixtures were fully characterized by high field ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and FTIR. Entries 4, 6 and 7 were fully characterized analytically as diastereomers. The ratio of compounds in entry 7 was determined by ^{1}H NMR (400 MHz) Entries 1, 2 and 7 were stirred at 25°C for 12 h then heated to 65°C for 12 h.

[b] No reaction at 65°C for 12 h.

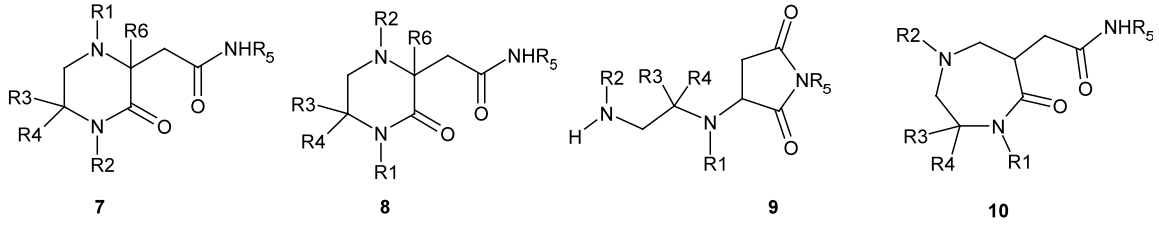

Figure 3. Products of the reaction of ethylene diamines with maleimides.

Table 3. Reaction of ethylenediamines with maleimides[a]

Entry	R1	R2	R3	R4	R5	R6	Yield (%)	**7**	**8**	**9**
1	Me	H	H	H	H	H	88[b]	100	0	–
2	Me	H	H	H	Ph	H	92[c]	100	0	–
3	H	H	Me	Me	Ph	H	84	100	0	–
4	H	Ph	H	H	Ph	H	65[d]	0	0	100
5	Me	Me	H	H	H	H	95	100[e]	–	–
6	Me	Me	H	H	Ph	H	69	100[e]	–	–
7	Me	Et	H	H	H	H	93	93	7	–
8	Me	Et	H	H	Ph	H	76	91	9	–
9	H	Me	H	H	Ph	Me	32[d,f]	100	0	–

[a] Ph = Phenyl. Me = Methyl. Et = Ethyl. All reactions carried out in EtOH at 25°C for 24 h unless noted. All compounds were fully characterized by high field ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and FTIR. Entries 7 and 8 were analytically characterized as mixtures and their ratios determined by ^{1}H NMR and ^{13}C NMR.

[b] Heated at 25°C for 2 h.

[c] Heated at 25°C for 12 h.

[d] Heated at reflux for 24 h.

[e] Note that in this case **7** and **8** are the same structure.

[f] Entry 9 is also accompanied by production of aniline (55%) and compound **10** (13%).

are based on the following spectral data: compound **7** (Table 3, entry 1) showed *N-Me* absorptions at 2.49 ppm (^{1}H NMR) and 43.0 ppm (^{13}C NMR) while compound **7** (Table 3, entry 5) showed absorptions for *N-Me* at 2.43 ppm (^{1}H NMR) and 43.2 ppm (^{13}C NMR) and for CO*N-Me at* 2.92 ppm (^{1}H NMR) and 34.6 ppm (^{13}C NMR), respectively. The *gem*-dimethyl EDA provided a clean, regiospecific product in which the least hindered end of the EDA added to the maleimide double bond with subsequent ring closure to the ketopiperazine (entry 3). Reaction of *N*-phenyl EDA afforded 1,4-addition of the more nucleophilic nitrogen, but did not give ketopiperazine ring closure presumably due to the lack of nucleophilicity of the phenyl substituted nitrogen (entry 4). *N*,*N*′-Dimethyl EDA gave Michael addition followed by facile ring opening of the *N*-phenyl or *N*-H maleimide (entries 5, 6). *N*-methyl-*N*′-ethyl EDA demonstrated the relative effect of *N*-methyl versus *N*-ethyl substitution of the EDA in reaction with maleimides (entries 7, 8). The reaction showed excellent regioselectivity (12:1 and 10:1 respectively) with the methyl substituted nitrogen adding preferentially in the initial 1,4-addition to the maleimide double bond. Reaction of *N*-methyl EDA

with a methyl substituted maleimide afforded aniline as the major product (55%) as well as the desired ketopiperazine (32%) and 13% of a product identified as the seven-membered ring compound **10** (entry 9). The latter presumably arises from initial isomerization of the vinyl methyl group to an *exo*-methylene moiety followed by 1,4-addition and ring formation.[4]

In summary we have explored the reaction of substituted EDAs with various fumarates maleates, citraconates and maleimides to form substituted ketopiperazine acetic acid esters and amides. The chemistry is synthetically useful and can yield surprising results with regard to regio- and stereoselectivity. We are continuing to explore this reaction in the formation of various ring sizes using other tethered binucleophiles (e.g. N,O; S,O; S,N) for application to the medicinal chemistry of peptidomimetics.

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References

1. (a) Shreder, K.; Zhang, L.; Gleeson, J.-P.; Ericsson, J. A.; Venkatachalapathi, V. Y.; Goodman, M. *J. Comb. Chem.* **1999**, *1*, 383; (b) Dinsmore, C. J.; Bergman, J. M.; Bogusky, M. J.; Culberson, J. C.; Hamilton, K. A.; Graham, S. L. *Org. Lett.* **2001**, *3*, 865.
2. (a) Petasis, N. A.; Patel, Z. D. *Tetrahedron Lett.* **2000**, *41*, 9607; (b) Beshore, D. C.; Dinsmore, C. J. *Org. Lett.* **2002**, *4*, 1201; (c) Dinsmore, C. J.; Zartman, C. B. *Tetrahedron Lett.* **2000**, *41*, 6309; (d) Cheng, J.-F.; Chen, M.; Arrhenius, T.; Nadzan, A. *Tetrahedron Lett.* **2002**, *43*, 6293; (e) Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K.; Phalgune, U. D. *Tetrahedron Lett.* **2002**, *43*, 1897.
3. (a) Phillips, A. P. US Pat. 2,958,693, 1960; *Chem. Abstr.* **1961**, *55*, 9437i; (b) Sheremeteva, T. V.; Sharifov, G. S.; Romashkova, K. A. *Dokl. Akad. Nauk SSSR* **1968**, *182*, 859; *Chem. Abstr.* **1969**, *70*, 37783d; (c) Masuzawa, K.; Masaki, M.; Ohta, M. *Chem. Pharm. Bull.* **1966**, *14*, 194; (d) Sharma, S.; Bindra, R.; Iyer, R. N.; Anand, N. *J. Med. Chem.* **1975**, *18*, 913; (e) Cantatore, G.; Borzatta, V. *Chem. Abstr.* **1989**, *111*, 116279n; (f) Gubert, S.; Braojos, C.; Anglada, L.; Bolos, J.; Sacristan, A.; Ortiz, J. A. *J. Heterocyclic Chem.* **1993**, *30*, 275; (g) Sheremeteva, T. V.; Kudryavtsev, V. V. *Izv. Akad. Nauk SSSR Ser. Khim.* **1966**, *2*, 289.
4. Cave′, C.; Gassama, A.; Mahuteau, J.; d'Angelo, J.; Riche, C. *Tetrahedron Lett.* **1997**, *38*, 4773.
5. A typical experimental follows for the preparation of compounds listed in Tables 1 and 2. Compound **5** (Table 2, entry 1): *Methyl 2-oxo-3-methyl-3-carboxymethyl-piperazine*: To a solution of EDA (0.67 mL, 10 mmol) in methanol (15 mL) at room temperature was added dimethyl citraconate (1.4 mL, 10 mmol). The reaction was stirred for 24 h then the methanol was reduced in vacuo to ca. 25% of its original volume. Ethyl ether was added and the resulting white precipitate was collected by filtration, and washed with more ether to afford 1.2 g (65%) of white solid, mp 128–130°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 2.20 (bs, 1H,), 2.50 (d, $J=16.7$ Hz, 1H), 3.00 (m, 1H), 3.05 (d, $J=16.7$ Hz, 1H), 3.12 (ddd, $J=13.6$, 10.1, 4.3 Hz, 1H), 3.28 (ddd, $J=11.7$, 7.0, 3.1 Hz, 1H), 3.47 (dddd, $J=11.7$, 7.8, 4.68, 1.17 Hz, 1H), 3.65 (s, 3H), 6.02 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 172.1, 57.6, 51.6, 43.8, 42.8, 38.2, 24.9; IR (KBr) 1718, 1664 cm^{-1}. Generally speaking, ketopiperazines with a secondary amide tended to be solids. The ketopiperazines with a tertiary amide tended to be oils that were easily purified by silica gel chromatography using 10% methanol/ethyl acetate as eluent.
6. A typical experimental follows for Table 3. Compound **7** (Table 3, entry 5): *1,4-Dimethyl-2-oxo-3-carboxamide methyl-piperazine*: To a solution of *N,N′*-dimethyl EDA (2.1 mL, 20 mmol) in ethanol (30 mL) at room temperature was added maleimide (1.9 g, 20 mmol). The reaction was stirred for 24 h and then the ethanol was reduced in vacuo to ca. 25% of its original volume. Ethyl ether was added, and the gummy mixture was triturated with a spatula. After several hours a precipitate formed which was collected by filtration and washed with more ethyl ether to afford 3.5 g (95%) of an off-white solid, mp 99–101°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.56 (ddd, $J=12.47$, 10.91, 3.9 Hz, 1H), 2.66 (dd, $J=15.6$, 5.0 Hz, 1H), 2.85 (dd, $J=15.6$, 3.5 Hz, 1H), 2.92 (s, 3H), 2.98 (dd, $J=4.3$, 2.7 Hz, 1H), 3.02 (t, $J=5.0$ Hz, 1H), 3.12 (dt, $J=11.7$, 3.6 Hz, 1H), 3.49 (ddd, $J=15.6$, 11.3, 4.3 Hz, 1H), 5.80 (bs, 1H), 7.00 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 168.3, 64.5, 50.6, 47.3, 43.0, 35.8, 34.5; IR (KBr) 1689, 1633 cm^{-1}.