Synthesis of Cyclohexa-1,3-dienamines by Formal [3+3] Cycloaddition

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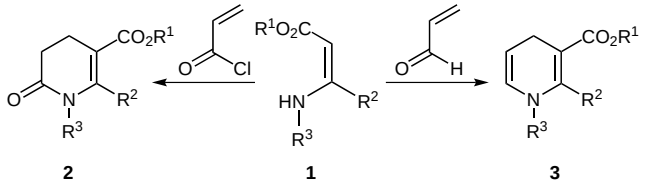
Abstract: Formal [3+3] cycloadditions of β-carboxymethylenamino esters with acrolein derivatives give a range of cyclohexa-2,6-dicarboxymethyl-1,3-dienamines that are potential acceptor–donor–acceptor systems.

Key words: multicomponent reactions, cyclohexa-1,3-dienamines, [3+3] cycloaddition, donor–acceptor systems

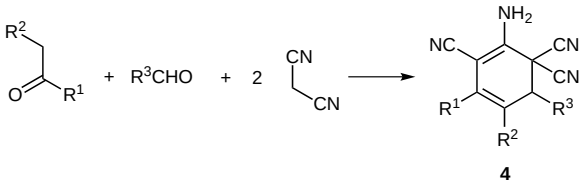
In a continuation of our investigations on the reactions of stabilized β-carboxymethyl enamines,[1] we were interested in their reaction with acrolein derivatives. It has been shown that primary and secondary enamines **1**, stabilized by a carbonyl group, react with electrophilic olefins[2] such as acrylic and acrolein derivatives to furnish, respectively, δ-lactams **2** and dihydropyridines **3**, through an intramolecular N-addition process (Scheme 1).



Scheme 1

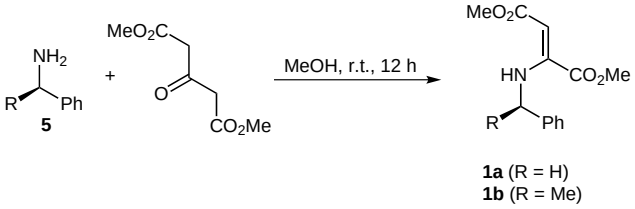
However, in the reaction starting from β-carboxymethylenamino esters (R′ = CH_2CO_2Me) with acrolein derivatives, we have observed the occurrence of both C- and N-annulation (Table 1). Herein, we would like to report the results of this study, which allow the construction of useful multifunctional molecules, cyclohexa-1,3-dienamines **7**, via a formal [3+3] cycloaddition. In almost all cases the reported syntheses of 2,6-substituted cyclohexa-1,3-dienamines involve the preparation of 2,6-tricarbonitrile compounds **4**, which were prepared by a one-pot multi-component cyclization process involving a ketone, an aldehyde, and usually two equivalents of malononitrile (Scheme 2).[3]

Compounds **4** belong to typical acceptor–donor–acceptor systems (A-D-A), which form the basis for artificial photosynthetic systems[4] and materials presenting semiconducting or nonlinear optical properties.[5] As a result, numerous publications report their syntheses.[3] However, one of the major problems associated with these syntheses is the β-elimination of HCN that occurs during the reaction, leading to the formation of aromatic products.[3c] Here we wish to present our results concerning the synthesis of analogues of **4**; cyclohexa-2,6-dicarboxymethyl-1,3-dienamines.



Scheme 2

The starting β-carboxymethylenamino esters (R^2 = CH_2CO_2Me) **1** were synthesized by condensation of dimethyl acetonedicarboxylate with a range of primary amines **5**. This reaction allowed the formation of *Z*- and *E*-enaminoesters **1** with the *Z*-diastereoisomers as major compounds (Scheme 3). We observed that the chemical shift of the NH proton for the major *Z*-stereoisomers was found downfield (δ = 8.5–9 ppm) from those of the *E*-stereoisomers (δ = 5–5.5 ppm). It is noteworthy that the two diastereoisomers are in equilibrium, the *E*-isomer being the kinetic product and the *Z*-isomer the thermodynamic product. An examination of the ^{1}H NMR spectra of isomers **1a** in $CDCl_3$ and in CD_2Cl_2 showed that after five minutes the *E*-isomer predominates (*Z*/*E* = 10:90). After 10 minutes the ratio decreased (*Z*/*E* = 38:62) and after 25 minutes the ratio was inverted (*Z*/*E* = 61:39). After three hours the equilibrium was reached in solution (*Z*/*E* = 80:20). Moreover, we noted that in solvents such as DMSO-d_6, in which intermolecular hydrogen bonds compete with intramolecular hydrogen bonds, the equilibrium was reached after five minutes, with the *E*-isomer remaining as the major isomer (*Z*/*E* = 19:81).



Scheme 3

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The crude mixtures of *Z*- and *E*-enaminoesters **1** (ratio after equilibration in CH_2Cl_2: *Z*/*E* for **1a** 80:20; *Z*/*E* for **1b** 87:13) were used in the cyclization using acrolein derivatives as the electrophilic olefin.[6]

The first reaction was performed by adding one equivalent of acrolein **6a** ($R^2 = R^3 = H$) to β-enaminoester **1a** ($R^1 = H$) in dichloromethane. The reaction mixture was stirred for 24 hours at room temperature and classical workup furnished a mixture of two products: the cyclohexa-1,3-dienamine **7a** and 2-hydroxytetrahydropyridine **8a**.[7] After chromatography on silica gel, the expected cyclohexa-1,3-dienamine **7a** was isolated in 39% yield (Table 1, entry 1). Only small amounts of product **8a** (3% yield) were obtained, suggesting a degradation of this compound on silica gel.

To optimize the reaction for the formation of cyclohexa-1,3-dienamine **7a**, various reaction conditions were investigated; the results are listed in Table 1 (entries 1–4). It would be interesting to test the reaction on both pure diastereoisomers *Z* and *E* but, unfortunately, the two isomers are in fast equilibrium (see above).

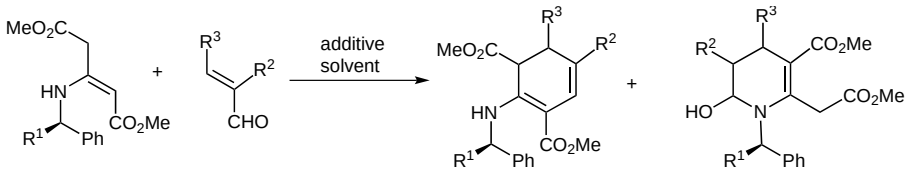
Solvents such as CH_2Cl_2, THF and pentane were tested and found to have a significant effect on the reaction outcome (Table 1, entries 1–3). In methanol a complex mixture of unidentified products was observed (data not shown). In CH_2Cl_2 and THF we observed by ^1H NMR analysis of the crude product, a mixture of compounds **7a** and **8a** in favor of dienamine **7a** (Table 1, entries 1 and 2). In less polar solvent such as pentane (entry 3), tetrahydropyridine **8a** was found to be the major product. Unfortunately, this latter product could only be purified in trace amounts. We believe that on silica gel, which is known to be acidic, compound **8a** is not stable and may be transformed into compound **7a**. Therefore, we followed the conversion of **8a** into 1,3-dienamine **7a** by ^1H NMR analysis in $CDCl_3$ using benzoic acid as catalyst. As expected, after one week, we observed complete conversion.

Thus, by slightly modifying the procedure (addition of a catalytic amount of benzoic acid to the reaction mixture; Table 1, entry 4) the yield of compound **7a** reached 49%. When using more acidic reagent such as APTS, only traces of product **7a** were observed in the crude reaction mixture (data not shown).

Substrate **1b** ($R^1 = Me$) gave the desired cyclohexa-1,3-dienamine **7b** in low yield as a 50:50 mixture of diastereoisomers (Table 1, entry 5). This result indicates that no asymmetric induction occurred.

We observed, by using electrophilic olefins such as methacrolein (Table 1, entry 6), crotonaldehyde (entry 7), or *trans* cinnamaldehyde (entry 8), the formation of the expected amino cyclohexadienes **7c**–**e** in moderate to good yields. The best yield and good diastereoselectivity in favor of the *trans* isomer was reached starting from crotonaldehyde (entry 7). In the case of cinnamaldehyde, only the *trans* isomer was observed and isolated. The stereochemical assignment of the two cyclohexadienes **7d** and **7e** (entries 7 and 8) was inferred by ^1H NMR spectroscopy (NOE experiments). For Table 1, entries 5–8, owing to the complexity of the ^1H NMR spectra of the crude mixtures (several diastereoisomers could be formed) and due to the small quantities formed and the instability of compounds **8** on silica gel, compounds **8b**–**e** could not be unambiguously identified and therefore no ratio was given for these entries.

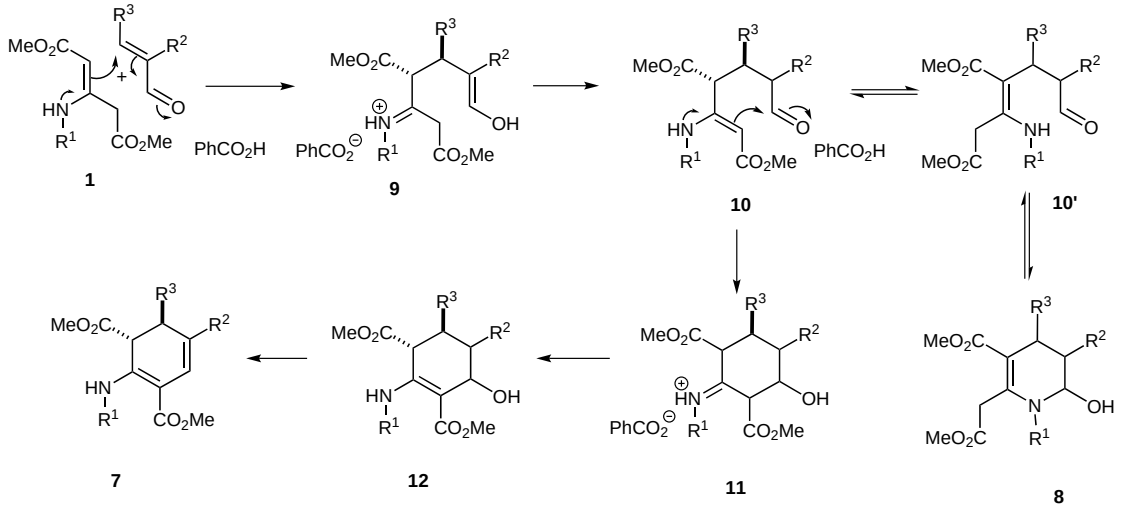
Table 1 Optimization of the Reaction Conditions



1 **6** **7** **8**

Entry	R^1	R^2	R^3	Additive (0.1 equiv)	Solvent	Ratio[a] **7**/**8**	Yield of **7** (%)[b]		d.r. of **7**[c]
1	H	H	H	–	CH_2Cl_2	54:46	**7a**	39	–
2	H	H	H	–	THF	66:34	–		–
3	H	H	H	–	pentane	30:70	–		–
4	H	H	H	benzoic acid	CH_2Cl_2	74:26	**7a**	49	–
5	Me	H	H	benzoic acid	CH_2Cl_2	–	**7b**	20	50:50
6	H	Me	H	benzoic acid	CH_2Cl_2	–	**7c**	35	–
7	H	H	Me	benzoic acid	CH_2Cl_2	–	**7d**	69	89:11
8	H	H	Ph	benzoic acid	CH_2Cl_2	–	**7e**	31	>95:5

[a] Ratio **7**/**8** determined by ^1H NMR analysis of the crude reaction mixture.
[b] Overall yield (two steps from **5**).
[c] Diastereoisomeric ratio determined by ^1H NMR analysis of the reaction mixture.



Scheme 4

A proposed mechanism for this formal [3+3] cycloaddition is presented in Scheme 4. This mechanism involves, in the first step, a Michael addition of enamine **1** to the unsaturated aldehyde. The resulting iminium **9** gives, by proton exchange, enamines **10** or **10′**. Intramolecular C-addition of **10** leads to iminium **11**, which, after proton exchange, equilibrates to 1-aminocyclohexene **12**. Water elimination leads to the expected aminocyclohexadiene **7**. Compounds **8** should arise from cyclization of the regioisomer **10′** by intramolecular N-addition. We saw that the acid-catalyzed opening of compound **8a** in $CDCl_3$ led to product **7a** (see above). This result indicates that it should be possible to reverse the reaction of N-cyclization, thus giving access to the more stable conjugated systems **7**.

We have developed a simple method for the synthesis of polysubstituted cyclohexa-1,3-dienamines by a formal [3+3] cycloaddition.[8] Moderate to good yields over the two steps, the use of simple starting materials, and the fact that the reaction can be carried out under mild conditions, are advantages of this method. Moreover, we have presented the first synthesis of analogues of tricyanocyclohexa-1,3-dienamines that are new one-donor poly-acceptors systems.

Acknowledgment

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(6) In all experiments we obtained about 120% of the expected weight.

(7) For recent publications concerning the synthesis of 2-hydroxytetrahydropyridines, see: (a) Ohba, M.; Natsutani, I. *Tetrahedron* **2007**, *63*, 12689. (b) Shen, L.; Cao, S.; Wu, J.; Li, H.; Zhang, J.; Wu, M.; Qian, X. *Tetrahedron Lett.* **2010**, *51*, 4866. (c) Kumar, R.; Kumar, D.; Prasad, A. K. *Synth. Commun.* **2011**, *41*, 2640. (d) Sun, J.; Wu, Q.; Xia, E. Y.; Yan, C. G. *Eur. J. Org. Chem.* **2011**, 2981.

(8) **Typical Procedure**: To a solution of dimethyl 3-benzylaminopent-2-enedioate (0.43 g, 1.6 mmol) in CH_2Cl_2 (7 mL) at 0 °C, was added aldehyde (0.11 mL, 1.6 mmol) and benzoic acid (0.020 g, 0.16 mmol) and the reaction mixture was stirred for 24 h. The mixture was poured into a solution of $NaHCO_3$, extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography to afford the cyclohexa-1,3-dienamine.
Dimethyl 2-Benzylamino-cyclohexa-1,5-diene-1,3-dicarboxylate (7a). IR (NaCl): 3348, 1735, 1655, 1595, 1436, 1224, 697 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.25

(ddt, J = 2.9, 6.9, 16.8 Hz, 1 H, C*H*H), 2.65 (ddd, J = 1.4, 6.3, 16.8 Hz, 1 H, CH*H*), 3.47 (dd, J = 1.4, 6.9 Hz, 1 H, CH_2CH), 3.57 (s, 3 H, CH_3), 3.67 (s, 3 H, CH_3), 4.45 (m, 2 H, $HNCH_2$), 5.23 (ddd, J = 2.9, 6.3, 9.4 Hz, 1 H, CH), 6.44 (dd, J = 2.9, 9.4 Hz, 1 H, CH), 7.20–7.43 (m, 5 H, PhH), 9.71 (m, 1 H, NH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 25.3, 40.0, 46.5, 50.2, 52.4, 92.9, 110.8, 124.5, 126.8, 127.5, 128.8, 137.7, 157.1, 168.8, 170.9. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NO_4$: 324.1212; found: 324.1206.

Dimethyl 2-[(1*R*)-Phenylethylamino]cyclohexa-1,5-diene-1,3-dicarboxylate (7b); Diastereoisomer 1: IR (NaCl): 3367, 1736, 1655, 1592, 1449, 1241, 756, 700 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.53 (d, J = 6.7 Hz, 3 H, CH_3), 1.96–2.08 (m, 1 H, CH*H*), 2.38–2.64 (m, 1 H, C*H*H), 3.24 (dd, J = 1.4, 6.8 Hz, 1 H, CH_2CH), 3.69 (s, 3 H, CH_3), 3.71 (s, 3 H, CH_3), 4.61–4.76 (m, 1 H, PhC*H*), 5.12–5.23 (m, 1 H, CH=C*H*), 6.42 (ddd, J = 3.1, 4.4, 9.7 Hz, 1 H, C*H*=CH), 7.21–7.33 (m, 5 H, PhH), 9.70 (d, J = 7.0 Hz, 1 H, NH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 25.0, 26.4, 40.7, 50.7, 52.7, 53.1, 92.9, 110.4, 124.9, 126.1, 127.3, 128.7, 144.2, 156.7, 169.1, 171.2.

Diastereoisomer 2: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.53 (d, J = 6.7 Hz, 3 H, CH_3), 2.38–2.64 (m, 2 H, CH_2), 3.12 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 3.55 (dd, J = 1.8, 7.0 Hz, 1 H, CH_2CH), 4.61–4.76 (m, 1 H, PhC*H*), 5.12–5.23 (m, 1 H, CH=C*H*), 6.42 (ddd, J = 3.1, 4.4, 9.7 Hz, 1 H, C*H*=CH), 7.21–7.33 (m, 5 H, PhH), 9.85 (d, J = 7.0 Hz, 1 H, NH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 25.2, 26.4, 40.2, 52.0, 52.8, 53.1, 93.2, 111.3, 124.5, 125.4, 127.4, 129.1, 144.1, 156.7, 169.1, 170.8. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{21}NO_4$: 338.1368; found: 338.1363

Methyl 2-Benzylamino-5-methyl-cyclohexa-1,5-diene-1,3-dicarboxylate (7c): IR (NaCl): 3385, 1733, 1654, 1592, 1436, 1215, 757, 668 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.79 (s, 3 H, CH_3), 2.29–2.52 (m, 2 H, CH_2), 3.75 (dd, J = 1.9, 6.4 Hz, 1 H, C*H*CO_2Me), 3.68 (s, 3 H, CH_3), 3.73 (s, 3 H, CO_2CH_3), 4.46–4.64 (m, 2 H, CH_2Ph), 6.20 (s, 1 H, C*H*), 7.13–7.38 (m, 5 H, PhH), 9.51–9.60 (m, 1 H, NH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 22.6, 30.3, 40.7, 46.7, 50.7, 52.6, 93.2, 118.3, 121.2, 126.9, 127.6, 128.9, 138.1, 155.5, 169.0, 171.3. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{21}NO_4$: 338.1368; found: 338.1363.

Dimethyl 2-Benzylamino-4-methyl-cyclohexa-1,5-diene-1,3-dicarboxylate (7d): IR (NaCl): 3389, 1731, 1659, 1601, 1437, 1215, 668 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (d, J = 7.2 Hz, 3 H, CH_3), 2.74–2.86 (m, 1 H, C*H*CH_3), 3.33 (s, 1 H, C*H*CO_2Me), 3.60 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, CO_2CH_3), 4.37–4.56 (m, 2 H, CH_2Ph), 5.23 (dd, J = 5.6, 9.8 Hz, 1 H, C*H*), 6.37 (d, J = 9.8 Hz, 1 H, CH), 7.20–7.36 (m, 5 H, PhH), 9.73–9.84 (m, 1 H, NH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.8, 30.9, 46.3, 46.9, 50.5, 52.4, 92.1, 116.8, 122.1, 126.9, 127.5, 128.7, 138.5, 155.5, 168.8, 170.7. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{21}NO_4$: 338.1368; found: 338.1363.

Dimethyl 2-Benzylamino-4-phenyl-cyclohexa-1,5-diene-1,3-dicarboxylate (7e): IR (NaCl): 3363, 1736, 1656, 1597, 1494, 1451, 1227, 699 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.56–3.59 (m, 1 H, C*H*CO_2Me), 3.62 (s, 3 H, CH_3), 3.66 (s, 3 H, CH_3), 3.99 (d, J = 6.2 Hz, 1 H, C*H*Ph), 4.19–4.37 (m, 2 H, CH_2Ph), 5.32 (ddd, J = 0.6, 6.1, 9.7 Hz, 1 H, CH=C*H*), 6.64 (d, J = 9.7 Hz, 1 H, C*H*=CH), 6.76–7.17 (m, 10 H, PhH), 9.61–9.66 (m, 1 H, NH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 41.4, 46.3, 48.4, 50.8, 53.0, 92.9, 113.6, 125.2, 126.5, 127.1, 127.3, 127.7, 128.7, 137.7, 140.1, 155.4, 168.9, 170.6. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{23}NO_4$: 400.1525; found: 400.1519.

Methyl 1-Benzyl-6-hydroxy-2-methoxycarbonylmethyl-1,4,5,6-tetrahydro-pyridine-3-carboxylate (8a): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.68–1.87 (m, 1 H, OHHCC*H*H), 1.96–2.10 (m, 1 H, HOHCCH*H*), 2.33–2.47 (m, 1 H, C*H*H), 2.67–2.77 (m, 1 H, CH*H*), 3.58 (d, J = 17.4 Hz, 1 H, C*H*HCO_2Me), 3.66 (s, 3 H, CH_3), 3.68 (s, 3 H, CH_3), 4.28 (d, J = 17.4 Hz, 1 H, CH*H*CO_2Me), 4.60 (q, J = 17.8 Hz, 2 H, PhCH_2), 4.80 (m, 1 H, C*H*OH), 7.13–7.37 (m, 5 H, PhH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 17.4, 27.6, 35.4, 50.9, 52.4, 52.1, 80.1, 98.7, 125.9, 127.3, 129.1, 138.2, 148.2, 168.7, 171.3. HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{21}NO_5$: 342.1317; found: 342.1312.

