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Diastereoselective addition of nitro compounds to α,β-unsaturated γ-butyrolactones

Giovanni B. Rosso and Ronaldo A. Pilli*

Instituto de Química, Universidade Estadual de Campinas, UNICAMP, PO Box 6154, 13083-970, Campinas, São Paulo, Brazil

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Abstract—Herein, we report our results on the diastereoselective addition of nitro compounds to α,β-unsaturated γ-butyrolactones, which afforded the corresponding Michael adducts **9**–**17** in moderate to good yields and good to excellent diastereoisomeric ratio. A one-pot conversion of α,β-unsaturated γ-butyrolactones **7** and **8** to the corresponding trisubstituted keto-γ-butyrolactones **24** and **25** via a tandem Michael–Nef protocol is also described.

The Michael addition reaction is one of the most important methods for carbon–carbon bond formation in organic synthesis,[1] and generally enolates derived from active methylene or methine compounds are used as nucleophiles under basic conditions. In this way, nitro compounds are synthetically useful due to the acidity of C–H bonds α to the nitro group and its easy transformation into a broad range of functionalities[2,3] as revealed by their application in the total synthesis of natural products[4] and biologically active compounds.[5]

A variety of reaction conditions including the use of amines, aqueous media, heterogeneous catalysis, microwave, ultrasound, and solvent-free media have been described for the reaction of nitro compounds with Michael acceptors.[1] The limited number of examples available in the literature[6] and the poor yields observed in the preparation of 4-nitromethyl-γ-butyrolactones[7] prompted us to investigate the conjugate addition of nitro derivatives to unsubstituted and substituted α,β-unsaturated γ-butyrolactones as an entry to the total synthesis of some *Stemona* alkaloids[8,9] and GABA analogues.[10]

Commercially available 2(5*H*)-furanone (**1**) and 3-methyl-2(5*H*)-furanone (**2**) were employed as starting materials for the preparation of substituted α,β-unsaturated γ-butyrolactones **5**–**8**. For that purpose, we initially examined the allylation and cyanoethylation of 2-triisopropylsilyloxyfurans **3** and **4**, prepared in 92% and 99% yield, respectively, from **1** and **2** as described elsewhere.[11] Reaction of the lithiated form of silyloxyfuran **3** with allyl bromide, followed by hydrolysis with aqueous HCl (10% v/v), afforded **5** in 76% yield (two steps). For the allylation of 3-methyl-5-allyl-2(5*H*)-furanone (**6**), we turned to the use of silver(I) trifluoracetate as Lewis acid which afforded **6** in 58% yield (Scheme 1).[12] Silyloxyfurans **3** and **4** proved to be competent Michael donors when reacting with acrylonitrile affording the cyanoethylation products **7** and **8** in 89% and 91% yield, respectively, when $BF_3{\cdot}OEt_2$ was employed as Lewis acid (Scheme 1).[13]

The Michael addition of nitro compounds to α,β-unsaturated γ-butyrolactones could be efficiently carried out with 10 mol % of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as catalyst in moderate to excellent yields as shown by the formation of nitrolactones **9** and **10** in 69% and 88% yield (Table 1, and Scheme 2) from **1**.[14] Due to the highly acidic nature of the nitroalkyl substituent, nitrolactone **10** was isolated as an equimolar mixture of diastereoisomers at the $CHNO_2$ stereogenic center.

When this experimental condition was employed in the reaction of lactone **2** ($R^1 = Me$, $R^2 = H$, entry 3) with nitromethane, Michael adduct **11** was obtained in poor yield (34%) and moderate (4:1 ratio) diastereomeric ratio as determined by ^1H NMR and gas chromatography analyses. The *trans* stereochemistry of the major isomer

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* Corresponding author. Tel.: +55 19 37883083; fax: +55 19 37883023; e-mail: pilli@iqm.unicamp.br

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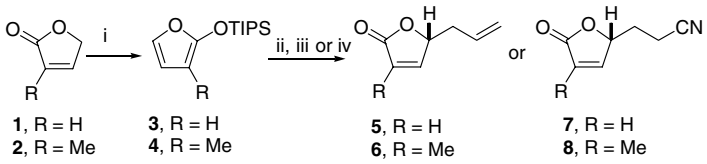
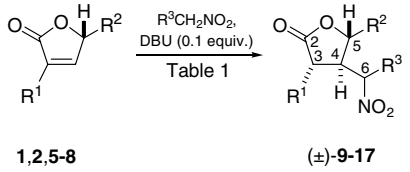


Scheme 1. Preparation of substituted γ-butyrolactones (+/−)-**5**–**8**. Reagents and conditions: for compound (+/−)-**5**: (i) **1**, TIPSOTf, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 92%; (ii) **3**, TMEDA, THF, *t*-BuLi, 2 h, 0 °C; then allyl bromide, 2 h, 0 °C to rt, HCl aq 10% (v/v), 76% (two steps); for compound (+/−)-**6**: (i) **2**, TIPSOTf, Et_3N, CH_2Cl_2, rt, 1.5 h, 99%; (iii) F_3CCO_2Ag, CH_2Cl_2, −78 °C; then **4**, CH_2Cl_2, allyl bromide, 1 h, −78 °C to rt, 58%; for compounds (+/−)-**7**, and (+/−)-**8**: (iv) **3** or **4**, acrylonitrile, CH_2Cl_2, −78 °C; then $BF_3{\cdot}OEt_2$, 2 h, −78 °C, (**7**, 89%); (**8**, 91%).

Table 1. Michael adducts derivatives (+/−)-**9**–**17** (Scheme 2)[a,b]

Entry	Lactone	Conditions	R^1	R^2	R^3	Nitrolactone	Yield (%)	3,4-*trans:cis* ratio	4,5-*trans:cis* ratio
1	**1**	16 h, rt	H	H	H	**9**	69	—	—
2	**1**	12 h, rt	H	H	CO_2Me	**10**	88	—	—
3	**2**	24 h, rt	CH_3	H	H	**11**	34	81:19	—
4	**2**	24 h, 60 °C	CH_3	H	H	**11**	75	89:11	—
5	**2**	24 h, rt	CH_3	H	CH_3	**12**	78	100:0	—
6	**2**	12 h, 60 °C	CH_3	H	CO_2Me	**13**	91	100:0	—
7	**5**	1 h, rt	H	Allyl	H	**14**	61	—	98:2
8	**6**	2 h, rt	CH_3	Allyl	H	**15**	68	100:0	100:0
9	**7**	4 h, rt	H	CH_2CH_2CN	H	**16**	88	—	100:0
10	**8**	1 h, rt	CH_3	CH_2CH_2CN	H	**17**	93	100:0	100:0

[a] The yields in Table 1 are based on isolated products (silica gel chromatography).
[b] The diastereoisomeric ratio was determined from the crude reaction by GC and proven by ^1H NMR data.



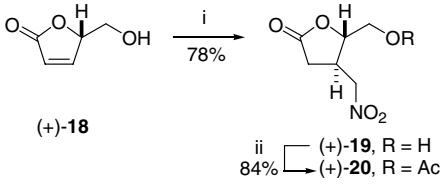
Scheme 2. Synthesis of nitrolactones (+/−)-**9**–**17** (see Table 1).

was established by inspection of the ^1H NMR spectrum of the mixture, which displayed the major methyl doublet less shielded (δ 1.33 ppm) than the minor isomer one (δ 1.22 ppm) in good agreement with the literature data reported for *cis*- and *trans*-**11** (δ 1.19 and 1.28 ppm, respectively).[15] Additionally, NOE experiments showed a 0.57% increment of the methyl doublet in the major isomer upon irradiation of H4 while no increment at H4 was observed when H3 was irradiated. Finally, the diastereoisomeric ratio and the yield were significantly improved (8:1 ratio and 75% yield, respectively) when the reaction was carried at 60 °C (entry 4). This observation corroborates the assignment of the *trans* configuration to the major stereoisomer and it is in line with the results by Costa and coworkers who described a quantitative epimerization of all *cis* 3,4,5-trisubstituted γ-butyrolactone to the corresponding 3,4-*trans* isomer upon treatment with DBU at rt.[16] The thermodynamically favored *trans*-nitrolactones **12** and **13** were formed as a 1:1 mixture of epimers at C6 in the addition of nitroethane and methyl nitroacetate, respectively, to lactone **2** (entries 5 and 6). The *trans* stereochemistry at C3–C4 was assumed based on the assignment previously described for γ-butyrolactone **11**.

When 5-allyl substituted lactone **5** was employed (entry 7), the corresponding adduct **14** was obtained as a 49:1 ratio of diastereoisomers at C4–C5. The same trend was observed when 5(2-ethylcyano) substituted lactone **7** was employed (entry 9). Complete 3,4-*trans*-4,5-*trans* diastereoselectivity and better yields were observed when 3,5-disubstituted lactones **6** and **8** (entries 8 and 10) were employed.

In order to unambiguously establish the *trans*-stereochemistry at C4 and C5 in the adducts obtained, we reacted (+)-5-hydroxymethyl-γ-butyrolactone **18**, prepared in four steps from D-(+)-mannitol as described in the literature by Mann and co-workers,[17] with nitromethane under the conditions described above to afford nitrolactone (+)-**19**[18] as a single diastereoisomer in 78% yield which was converted to (+)-**20** in 84% yield after acetylation with $Ac_2O/HClO_4$ (Scheme 3).

Unfortunately, the H5 signal in the ^1H NMR spectrum of (+)-**20** appeared overlapped making it difficult to compare it with the corresponding *cis* isomer described in the literature.[19] Although the H5 diagnostic signal



Scheme 3. Synthesis of chiral nitrolactones. Reagents and conditions: (i) CH_3NO_2, DBU 0.1 equiv, 4 h, rt; (ii) $HClO_4$, Ac_2O, 1 h, rt.

appears in a distinct spectral region in compound (+)-**19**, the NMR data for the corresponding 4,5-*cis* nitrolactone (+)-**21** was not available in the literature. In order to unambiguously establish the relative stereochemistry of Michael adducts (+)-**19** and (+)-**20**, we have prepared 4,5-*cis*-nitrolactone (+)-**21** according to the procedure described by Costa and co-workers.[19] Not only the ^{1}H NMR spectra of compounds (+)-**19** and (+)-**21** are clearly distinguishable but differential NOE experiments have firmly established their *trans*- and *cis*-4,5 relative stereochemistry, respectively (Fig. 1). Based on these results, the *trans* relationship for H4 and H5 was assumed for compounds **14**–**17**.

The approach described above was successfully implemented for the preparation of ketolactones **24** and **25**, which are key intermediates in our approach to *Stemona* alkaloids.[8,9]

DBU-catalyzed addition of methyl 4-nitrobutanoate to γ-butyrolactones **7** and **8** in refluxing acetonitrile afforded the corresponding nitrolactones **22** and **23** in moderate yield (60% and 62% yield, respectively) as a 1:1 mixture of epimers at the nitromethine carbon. Nef oxidation[3] of each mixture of nitrolactones with $KMnO_4$ adsorbed on silica gel (0.2 mmol of $KMnO_4$/g of silica gel) in refluxing benzene provided ketolactones **24** and **25**, in 45% and 42% yield, respectively (Scheme 4).

The preparation of ketolactones **24** and **25** could be achieved in a one-pot procedure by combining the DBU-catalyzed Michael addition of nitroesters to γ-butyrolactones and the use of DBU for the Nef reaction

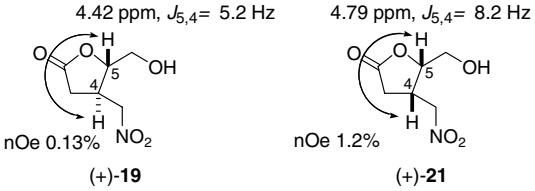
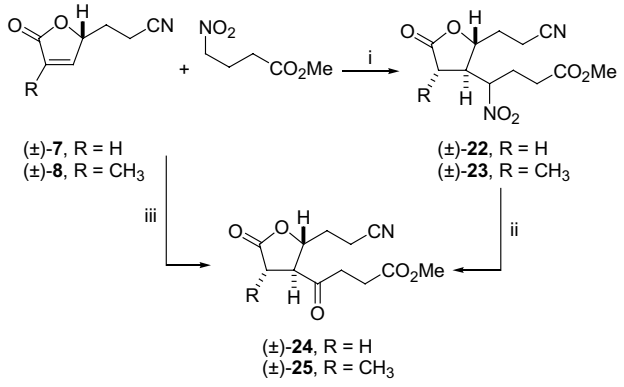


Figure 1. Differential NOE and coupling constants measurements on lactones (+)-**19** and (+)-**21**.



Scheme 4. Synthesis of (+/−)-**24** and (+/−)-**25**. Reagents and conditions: (i) DBU (0.1 equiv), CH_3CN, reflux; (**22**, 60%; **23**, 62%); (ii) $KMnO_4/SiO_2$, C_6H_6, reflux; (**24**, 45%; **25**, 42%) (iii) DBU (2 equiv), CH_3CN, reflux; (**24**, 30%; **25**, 35%).

described by Ballini and co-workers.[4] In the event, treatment of nitro compounds **7** and **8** with methyl 4-nitrobutanoate and excess DBU (2.0 equiv) in refluxing acetonitrile afforded ketolactones **24** and **25** in 30% and 35% overall yields, respectively.

In summary, the utility of the addition of silyloxyfurans to acrylonitrile and of nitro compounds to γ-butyrolactones has been demonstrated. The synthetic route described can be considered as an alternative method to synthesis cyclic GABA analogues and studies toward the stereoselective total synthesis of *Stemona* alkaloids employing this synthetic methodology are currently underway in our laboratory and will be reported in due course.

Acknowledgement

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Supplementary data

Characterization data, ^{1}H and ^{13}C NMR spectra for compounds **5**–**25** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.163.

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13. A typical procedure follows: To a stirred solution of 2-(triisopropylsilyloxy)furan **3** (0.17 g, 0.66 mmol) and previously distilled acrylonitrile (0.060 g, 1.05 mmol) in anhydrous CH_2Cl_2 (3 mL) at −78 °C and under an argon atmosphere was slowly added $BF_3{\cdot}OEt_2$ (0.12 g, 0.84 mmol) dropwise. The reaction was monitored by TLC and after completion, aqueous satd. $NaHCO_3$ (15 mL) was added. The solution was washed with CH_2Cl_2 (3×20 mL), the organic phase extracted, dried ($MgSO_4$), filtered and evaporated under vacuo to afford a crude oil. The resulting crude product was purified by chromatography silica column (hexanes/ethyl acetate 1:1) yielding **7** as a colorless oil (0.08 g, 89% yield). IR (neat): 3097, 2940, 2248, 1747, 1602, 1427, 1335, 1165, 1109 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.53 (dd, $^3J = 1.5$, $^3J = 5.8$, 1H), 6.22 (dd, $^4J = 2.1$, $^3J = 5.8$, 1H), 5.18 (dddd, $^2J = 1.8$, $^3J = 3.7$, $^3J = 6.1$, $^3J = 8.6$, 1H), 2.60 (ddd, $^3J = 7.1$, $^3J = 8.3$, $^2J = 17.2$, 1H), 2.55 (ddd, $^3J = 5.9$, $^3J = 7.2$, $^2J = 17.2$, 1H), 2.28 (dddd, $^3J = 3.7$, $^3J = 7.2$, $^3J = 8.4$, $^2J = 14.4$, 1H), 1.92 (dddd, $^3J = 5.8$, $^3J = 7.3$, $^3J = 8.7$, $^2J = 14.4$, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.9, 154.6, 122.6, 118.4, 80.6, 29.1, 13.4. HRMS (IE, 70 eV) *m/z*: calcd for $C_8H_{10}O_2$ $[M]^+$: 137.0477, found 137.0353 $[M]^+$.
14. Representative experimental procedure for **9**: To a stirred solution of 2(5*H*)-furanone (**1**) (0.42 g, 5.0 mmol) and CH_3NO_2 (18.9 g, 310 mmol) was added DBU (7.5 mg, 0.5 mmol) at rt. The resulting orange solution was stirred for an additional 16 h at rt. The crude was evaporated under reduced pressure to remove the excess of CH_3NO_2 and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate 1:1) without any extractions, yielding 0.50 g of **9** (69 %) as an oil. IR (neat): 3022, 2920, 1774, 1732, 1560, 1421, 1382, 1176, 1025, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.58 (dd, $^3J = 7.4$, $^2J = 9.8$, 1H), 4.54 (dd, $^2J = 2.0$, $^3J = 7.4$, 2H), 4.16 (dd, $^3J = 6.4$, $^2J = 9.8$, 1H), 3.38 (m, 1H), 2.82 (dd, $^3J = 8.9$, $^2J = 17.7$, 1H), 2.38 (dd, $^3J = 7.4$, $^2J = 17.7$, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.4, 76.1, 69.9, 33.5, 31.5. HRMS (IE, 70 eV) *m/z*: calcd for $C_5H_7NO_4$ $[M]^+$: 145.0375, found 145.0392 $[M]^+$.
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18. Analytical data for (4*R*,5*S*)-4-nitromethyl-5-hidroxymethyl-2-(5*H*)-furanone, (+)-**19**: $[\alpha]_D^{25}$ +0.2 (*c* 0.7, MeOH). IR (neat): 3422, 2937, 1772, 1635, 1557, 1428, 1383, 1197, 1080, 1032, 940 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.59 (dd, $^3J = 7.6$, $^2J = 13.7$, 1H), 4.51 (dd, $^3J = 7.0$, $^2J = 13.4$, 1H), 4.42 (dt, $^3J = 3.1$, $^3J = 5.2$, 1H), 3.99 (ddd, $^3J = 3.2$, $^3J = 4.7$, $^3J = 12.3$, 1H), 3.79 (ddd, $^3J = 3.1$, $^3J = 6.0$, $^2J = 12.3$, 1H), 3.31–3.39 (m, 1H), 3.01 (dd, $^3J = 9.9$, $^3J = 18.0$, 1H), 2.42 (dd, $^3J = 6.3$, $^2J = 18.2$, 1H), 2.27 (t, $^3J = 5.3$, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.3, 81.6, 76.4, 63.1, 34.8, 32.5.
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