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L-Proline-Catalyzed Three-Component Domino [3+2+1] Annulation for the Regio- and Diastereoselective Synthesis of Highly Substituted Thienothiopyrans Containing Three or Four Stereocenters

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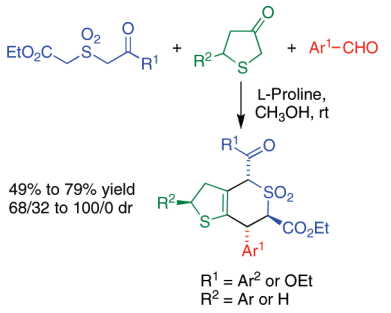

L-Proline-catalyzed three-component reactions of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate or ethyl 2-[(2-ethoxy-2-oxoethyl)sulfonyl]acetate, aromatic aldehydes, and 5-aryltetrahydro-3-thiophenone furnished a variety of highly substituted thieno[3,2-*c*]thiopyran derivatives. This facile transformation presumably occurs via a one-pot domino sequence of enamine formation/aldol condensation/Michael addition/6-*exo*-*trig* cyclization/elimination and involves the creation in a single operation of three C−C bonds and the generation of three new stereocenters with complete diastereoselectivity in all cases and a fourth one in ca. 7:3 diastereomeric ratio when starting from a 5-substituted tetrahydro-3-thiophenone derivative.

Cyclic sulfides are useful templates to facilitate and control various chemical transformations.[1] In particular, thiopyran derived scaffolds have been used to construct a variety of synthetic targets.[2] Members of the thienothiopyran class have attracted much interest since they were reported to possess antiglaucoma activity.[3] In fact, Trusopt (dorzolamide hydrochloride) is one of the most popular topically active carbonic anhydrase inhibitors (CAI), which causes a decrease in the aqueous humor secretion and therefore reduction of the intraocular pressure.[4] Furthermore, compounds with thiophene substructures have found remarkable applications as electroactive and light-emitting materials in a variety of opto-electronic devices and optical transducers in biosensors as well as fluorescent markers for biopolymers.[5]

The biological importance of thienothiopyrans, in conjunction with our interest in novel domino processes in organic synthesis,[6] led us to study the synthesis of thienothiopyrans **4**−**17** employing L-proline as a catalyst. This choice was prompted by the fact that L-proline is an abundant and inexpensive amino acid capable of catalyzing diverse organic transformations, in both enantio- and nonenantioselective fashions, including aldol,[7] Mannich,[8] Michael,[9] and unsymmetric Biginelli[10] reactions as well as Diels−Alder/Knoevenagel[11] and other domino processes.[12] The efficacy of L-proline in diverse organic transformations is ascribable to multiple catalytic roles it can play, such as an acid or a base or both simultaneously, as a nucleophile and its ability to form enamine/iminium intermediates upon reaction with carbonyl/α,*β*-unsaturated carbonyl compounds.

Stirring at room temperature for 24 h a solution of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate or ethyl 2-[(2-ethoxy-2-oxoethyl)sulfonyl]acetate **1**, a 5-aryltetrahydro-3-thiophenone derivative **2** (R^2 = Ar),[13] and an aromatic aldehyde **3** in an equimolar ratio in the presence of L-proline (50 mol %) in methanol furnished the thieno[3,2-*c*]thiopyran derivatives

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SCHEME 1. Synthesis of Thienothiopyrans

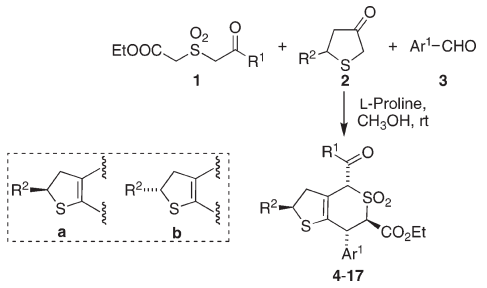

TABLE 1. Scope, Yields, and Diastereomeric Excesses in the Synthesis of Thienothiopyrans 4−17

compd	R^1	R^2	Ar^1	yield, %	dr[a]
4	*p*-ClC_6H_4	*p*-$H_3CC_6H_4$	*p*-$H_3CC_6H_4$	65	69/31
5	*p*-ClC_6H_4	*p*-$H_3CC_6H_4$	*p*-ClC_6H_4	60	68/32
6	*p*-ClC_6H_4	C_6H_5	*m*-FC_6H_4	52	71/29
7	*p*-ClC_6H_4	C_6H_5	*p*-$H_3COC_6H_4$	51	68/32
8	*p*-ClC_6H_4	*p*-ClC_6H_4	*p*-$H_3CC_6H_4$	49	73/27
9	OEt	*p*-$H_3CC_6H_4$	*p*-ClC_6H_4	76	70/30
10	OEt	C_6H_5	*p*-FC_6H_4	79	68/32
11	OEt	C_6H_5	*o*-$H_3CC_6H_4$	63	76/24
12	OEt	*p*-ClC_6H_4	C_6H_5	58	78/22
13	OEt	*p*-ClC_6H_4	*p*-$O_2NC_6H_4$	75	69/31
14	*p*-ClC_6H_4	H	C_6H_5	62	100/0
15	*p*-ClC_6H_4	H	*o*-$H_3CC_6H_4$	65	100/0
16	OEt	H	*o*-BrC_6H_4	64	100/0
17	OEt	H	*p*-$H_3CC_6H_4$	71	100/0

[a]The major diastereomer of compounds **4**−**13** had the structure **a**.

4−**13**, bearing four stereocenters, in 49−79% yields as mixtures of two diastereomers in ca. 7/3 ratio (Scheme 1, Table 1). Remarkably, although thienothiopyrans **4**−**13** have four stereocenters and hence eight diastereomers would be possible in principle, only two diastereomers, **4a**−**13a** and **4b**−**13b**, have been obtained, the former being highly predominating. These diastereomers (compounds **4a**−**13a** and **4b**−**13b**) could be separated in pure form by flash column chromatography. As expected, those reactions involving the use of tetrahydro-3-thiophenone **2** (R^2 = H) afforded the corresponding compounds **14**−**17** as single diastereomers in 62−71% yield (Scheme 1). Chiral HPLC analysis of thienothiopyran **4a** proved that this compound was almost racemic, the enantiomeric ratio being 50.7:49.3, and this showed that the reaction takes place essentially in a nonenantioselective way.

The reaction was very sensitive to the nature of the solvent employed as shown for the preparation of **4** (Table 2). Thus, it proceeded most efficiently in methanol, while it did not occur at all in ethanol. Thienothiopyrans were also obtained when DMF, DMSO, THF, and CH_3CN were employed as solvents, albeit in lower yields in methanol. Interestingly, the choice of basic catalyst also proved to be critical for the success of the reaction. As shown in Scheme 2 and Table 2, thienothiopyrans **4** were obtained only from the proline-catalyzed reactions. When pyrrolidine was used instead, the only product, isolated in 72% yield, was compound **18**,[14] arising from a double aldol condensation of compounds **2** and **3**, while triethylamine or DBU led to the formation of 1-(4-chlorophenyl)-2-(methylsulfonyl)-1-ethanone **19** and pyridine failed to catalyze any reaction (Table 3).

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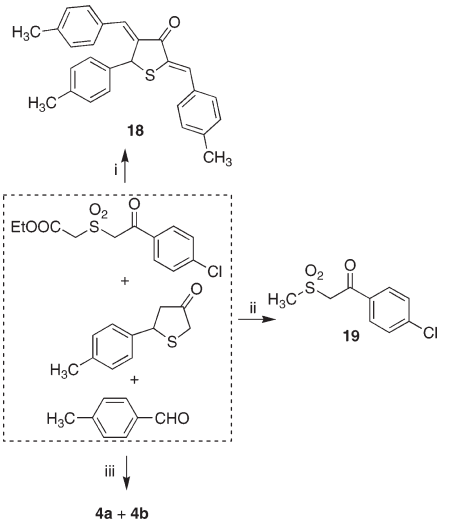
TABLE 2. Base-Mediated Product Selectivity and Solvent Effect on the Three-Component Domino Reactions

entry	base (50 mol %)	solvent	product	yield, %
1	pyrrolidine	methanol	**18**	72
2	Et_3N	methanol	**19**	48
3	DBU	methanol	**19**	56
4	pyridine	methanol	no reaction	no reaction
5	L-proline	methanol	**4**	65
6	L-proline	ethanol	no reaction	no reaction
7	L-proline	DMF	**4**	35
8	L-proline	DMSO	**4**	38
9	L-proline	CH_3CN	**4**	50
10	L-proline	THF	**4**	45

SCHEME 2. Influence of the Basic Catalyst on the Results of the Three-Component Domino Reaction[a]



[a]Reagents and conditions: (i) pyrrolidine, CH_3OH, rt; (ii) Et_3N, or DBU, CH_3OH, rt; (iii) L-Pro, CH_3OH, rt.

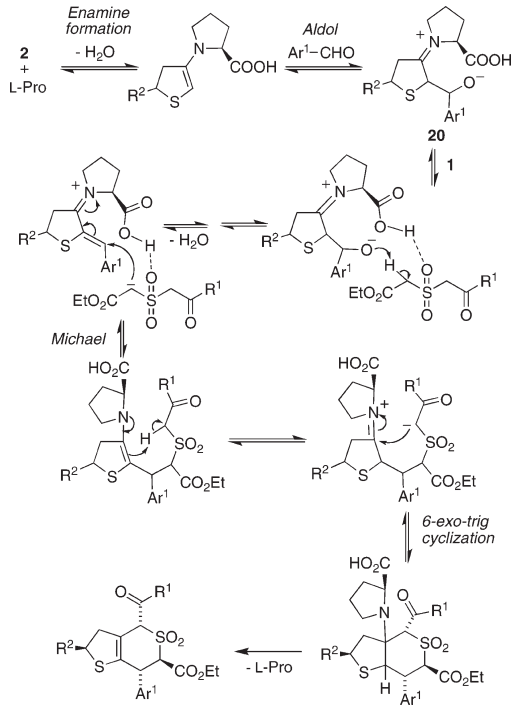
TABLE 3. Base-Mediated Product Selectivity of the Three-Component Domino Reaction

entry	base (50 mol %)	product	yield, %
1	pyrrolidine	**18**	72
2	Et_3N	**19**	48
3	DBU	**19**	56
4	L-proline	**4**	65
5	pyridine	no reaction	no reaction

The structure of thienothiopyrans **4** was deduced from one- and two-dimensional NMR spectroscopic data of **4a**, **4b**, and **14** and confirmed by single crystal X-ray diffraction studies of **4a** and **9a** (see the Supporting Information).

The mechanism proposed for the formation of thienothiopyrans **4**−**17** (Scheme 3) is in agreement with the fact that only L-proline catalyzes the domino reactions affording the thienothiopyrans, while the other bases led to either **18** or **19**. This may be taken as indirect evidence for the involvement of iminium intermediate **20**, which is presumably endowed with enhanced reactivity arising from (i) polarization of the C=C bond by the positively charged nitrogen of the iminium functionality and (ii) the probable hydrogen bonding between the carboxyl hydrogen and sulfonyl/carbonyl oxygens. This hydrogen bonding facilitates the Michael addition

SCHEME 3. Mechanistic Proposal for the Formation of 4-17



by bringing the aldol product closer to compound **1**; this assistance is obviously absent in the pyrrolidine-catalyzed reaction, which leads simply to the double aldol product **18**. Also, this hypothesis provides an explanation for the observed regioselectivity in favor of the Michael attack from the less acidic position in compound **1**, which can be accounted for by assuming that **1** approaches **20** so that its less hindered end is close to the Ar^1 substituent. When tertiary amines (triethylamine, DBU) are employed as bases, these enamine-initiated processes are not possible, and the only observed product is **19** arising from hydrolysis/decarboxylation of the ester group in compound **1**, probably by hydroxide anion generated from the bases and traces of water in the reaction media.

Presumably, the observed products are favored on thermodynamic grounds since they are more stable than other possible diastereoisomers because (i) the aryl ring at C-7 and the ester group at C-6 are in a trans-relationship and (ii) the aroyl group at C-4 and the ester group at C-6 are also in a trans-relationship to minimize interactions. Furthermore, in compounds **4a**−**13a** the aryl ring at C-2 and the proximate aroyl/aryl at C-4 and C-7 respectively are also in a trans-relationship, while in the minor diastereomers **4b**−**13b** this relationship is cis. However, semiempirical (AM1) calculations (MacSpartan 04) indicate that compound **9a** is only 0.27 kcal·mol^{-1} more stable than **9b**, and this similar stability explains the relatively modest **a**/**b** diastereoselectivity that we have encountered.

In conclusion, the present study reports a unique one-pot, three-component diastereoselective synthesis of thieno[3,2-*c*]thiopyrans, structurally related to pharmaceutically relevant compounds via a formal [3+2+1]annulation. This novel transformation involves a domino process comprising up to nine individual steps that include an aldol condensation, a Michael addition, and a 6-*exo*-*trig* ring-closing reaction and creates three carbon−carbon bonds with complete regioselectivity. Furthermore, this transformation generates three stereocenters that are completely controlled when starting from tetrahydro-3-thiophenone and a fourth one in ca. 7:3 diastereomeric ratio starting from a 5-substituted tetrahydro-3-thiophenone derivative. Finally, the synthetic process described here is attractive from an environmental point of view, as it requires only simple and readily available starting materials and an inexpensive and nontoxic catalyst (L-proline), and has water as the only side product.

Experimental Section

Synthesis of Thienothiopyrans: General Procedure. A mixture of ethyl 2-[(2-oxo-2-arylethyl)sulfonyl]acetate/ethyl 2-[(2-ethoxy-2-oxoethyl)sulfonyl]acetate (1.6 mmol), aromatic aldehyde (1.6 mmol), 5-aryltetrahydro-3-thiophenone (1.6 mmol), and L-proline (50 mol %) in methanol was stirred at room temperature for 24 h. Then the reaction mixture was extracted with CH_2Cl_2 (35 mL). The combined organic extracts were washed successively with water (25 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The diastereomers were separated and isolated in pure form by flash chromatography on siliga gel with petroleum ether−ethyl acetate mixture (47:3 v/v) as eluent. Data for two representative examples are given below. Full characterization data for all compounds can be found in the Supporting Information.

(2*R,4*R**,6*R**,7*R**)-Ethyl 4-(4-chlorobenzoyl)-2,7-di(4-methylphenyl)-5,5-dioxo-3,4,5,6,7-tetrahydro-2*H*-thieno[3,2-*c*]thiopyran-6-carboxylate (4a):** isolated as a colorless solid (0.430 g, 45%); mp 186 °C; IR ν_{max} (KBr) 1730, 1647, 1339, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.11 (3H, t, J = 7.1 Hz, $COOCH_2CH_3$), 2.33 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.86 (1H, ddd, J = 15.9, 5.3, 3 Hz, 3-CH_2), 3.26 (1H, ddd, J = 15.9, 9.6, 3 Hz, 3-CH_2), 4.05−4.19 (2H, m, $COOCH_2CH_3$), 4.60−4.65 (2H, m, 2-C*H* and 7-C*H*), 4.81 (1H, d, J = 11.4 Hz, 6-C*H*), 5.51 (1H, s, 4-C*H*), 7.12 (2H, d, J = 8.1 Hz, Ar), 7.19−7.24 (4H, m, Ar), 7.35 (2H, d, J = 8.1 Hz, Ar), 7.55 (2H, d, J = 8.1 Hz, Ar), 8.04 (2H, d, J = 8.7 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.8, 21.0, 21.2, 46.5, 48.5, 49.4, 62.9, 65.0, 66.2, 116.3, 126.5, 128.6, 129.5, 129.6, 130.8, 133.7, 134.1, 137.6, 138.5, 139.6, 140.3, 141.8, 162.2, 189.4; ee 1.4% determined by HPLC [CHIRALCEL OD-H column; hexane:2-propanol [95:5 (v/v)]; flow rate 0.5 mL/min; λ = 254 nm; t_R(major) = 48.98 min; t_R(minor) = 65.34 min]. Anal. Calcd for $C_{31}H_{29}ClO_5S_2$: C, 64.07; H, 5.03. Found: C, 64.12; H, 4.97.

(2*S,4*R**,6*R**,7*R**)-Ethyl 4-(4-chlorobenzoyl)-2,7-di(4-methylphenyl)-5,5-dioxo-3,4,5,6,7-tetrahydro-2*H*-thieno[3,2-*c*]thiopyran-6-carboxylate (4b):** isolated as an oily liquid (0.191 g, 20%); IR ν_{max} (CH_2Cl_2) 1732, 1680, 1277, 1121 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.08 (3H, t, J = 7.1 Hz, $COOCH_2CH_3$), 2.28 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.87−3.07 (2H, m, 3-CH_2), 4.00−4.21 (2H, m, $COOCH_2CH_3$), 4.46−4.55 (1H, m, 7-C*H*), 4.78 (1H, d, J = 11.1 Hz, 6-C*H*), 4.92 (1H, t, J = 9.3 Hz, 2-C*H*), 5.56 (1H, s, 4-C*H*), 7.06 (2H, d, J = 8.1 Hz, Ar), 7.15−7.21 (4H, m, Ar), 7.33 (2H, d, J = 7.8 Hz, Ar), 7.53 (2H, d, J = 8.7 Hz, Ar), 8.03 (2H, d, J = 8.7 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.8, 21.0, 21.2, 46.5, 48.0, 51.0, 62.9, 65.2, 66.3, 116.7, 127.0, 128.7, 129.3, 129.5, 129.6, 130.8, 133.5, 134.2, 137.5, 137.7, 138.4,

140.8, 141.8, 162.1, 189.2. Anal. Calcd for $C_{31}H_{29}ClO_5S_2$: C, 64.07; H, 5.03. Found: C, 64.13; H, 4.96.

(4*R,6*R**,7*R**)-Ethyl 4-(4-chlorobenzoyl)-5,5-dioxo-7-phenyl-2,3,4,5,6,7-hexahydro-5-thieno[3,2-*c*]thiopyran-6-carboxylate (14):** isolated as a pale yellow solid (0.487 g, 62%); mp 164 °C; IR ν_{max} (KBr) 1739, 1679, 1315, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.03 (3H, t, J = 7.1 Hz, $COOCH_2CH_3$), 2.72−2.79 (2H, m, 3-CH_2), 3.03−3.11 (1H, m, 2-CH_2), 3.16−3.26 (1H, m, 2-CH_2), 4.04−4.11 (2H, m, $COOCH_2CH_3$), 4.52 (1H, d, J = 11.3 Hz, 7-C*H*), 4.74 (1H, d, J = 11.3 Hz, 6-C*H*), 5.55 (1H, s, 4-C*H*), 7.35−7.44 (5H, m, Ar), 7.54 (2H, d, J = 8.7 Hz, Ar), 8.03 (2H, d, J = 8.7 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.8, 30.0, 39.8, 46.8, 62.8, 64.8, 66.2, 118.6, 128.6, 128.8, 128.9, 129.5, 130.8, 134.1, 136.8, 140.6, 141.8, 162.2, 189.3. Anal. Calcd for $C_{23}H_{21}ClO_5S_2$: C, 57.91; H, 4.44. Found: C, 57.86; H, 4.51.

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Supporting Information Available: Experimental procedures, analytical data, structural study of compounds **4a**, **4b**, and **14** by NMR, X-ray crystallographic determination of compounds **4a** and **9a**, copies of chiral chromatogram of **4a**, and ^1H, ^{13}C, and 2D NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.