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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7545–7549

Thiophenol-mediated improvement of the Pictet–Spengler cyclization of *N*-tosyl-β-phenethylamines with aldehydes

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Received 15 August 2006; revised 22 August 2006; accepted 23 August 2006

Abstract—The Lewis acid-catalyzed Pictet–Spengler condensation of *N*-tosyl-β-phenethylamines with aldehydes is improved by the addition of thiophenol, furnishing better yields of 1-substituted tetrahydroisoquinolines at a given time.

The Pictet–Spengler condensation of β-arylethylamines with aldehydes and ketones as carbonyl components is now established as one of the most powerful methods toward the synthesis of 1,2,3,4-tetrahydroisoquinolines (THIQ) and 1,2,3,4-tetrahydro-β-carbolines (THBC);[1] other nitrogen heterocycles have also been prepared employing this strategy.[2] One of the useful variations of the Pictet–Spengler reaction entails the use of electron withdrawing groups, such as acyl or sulfonyl moieties, bound to the starting β-arylethylamine. This allows the convenient preparation of certain otherwise inaccessible heterocycles, including optically active compounds.[3] Masked carbonyls, among them acetals, enol ethers, as well as α-halo-α-phenylthio-, α-halo-α-phenylseleno- and similar derivatives have also been employed as equivalents of the carbonyl component.[4] It is noteworthy that Comins and Badawi reported that an enolether, being more reactive than the corresponding aldehyde, underwent a Pictet–Spengler reaction under conditions where the aldehyde itself failed to react.[5a]

Additives able to modify in situ the reactivity of the carbonyl component have shown to have a profound influence on the yield of different cyclizations involving aldehydes. MacLean and Cundasawmy[5b] effected a Bobbitt-type cyclization in an aqueous-ethanolic medium and the group of Ogasawara and co-workers[5c] more recently disclosed that the electrophilic cyclization of an aldehyde onto an aromatic ring in a morphine intermediate could be successfully effected in the presence of ethyleneglycol, which actively participated in the reaction mechanism, seeming to be essential to accelerate the reaction and improve the yields. In addition, during the synthesis of an analog of the stephaoxocane alkaloids eletefine and stephaoxocanidine, we observed that the addition of ethanol was key to the success of the Jackson-type cyclization of an *N*-tosylaminoaldehyde into a 1,2-dihydroisoquinoline derivative, the aldehyde itself being completely unreactive in the absence of the alcohol.[5d] Finally, Ito and Tanaka reported that condensation of *N*-tosyl-3,4-dimethoxyphenethylamine with 4-bromobenzaldehyde and piperonal required prolonged reflux conditions in chloroform and toluene, respectively.[6] In connection with our ongoing research on the synthesis of tetrahydroisoquinolines employing organochalcogen derivatives, we have recently reported the Pictet–Spengler reaction of *N*-sulfonyl-β-arylethylamines with thioorthoesters as carbonyl components,[7] and were further interested in studying the Pictet–Spengler condensation of these sulfonamides with the chemically related phenylthioacetals.

As expected, we observed that the Pictet–Spengler condensation of *N*-sulfonyl-3,4-dimethoxyphenethylamine with the phenylthioacetal of benzaldehyde went to completion much faster than with the corresponding aldehyde (Scheme 1). Since the synthesis of phenylthioacetals involves the reaction of thiophenol with aldehydes under Lewis acid catalysis,[8] we supposed that

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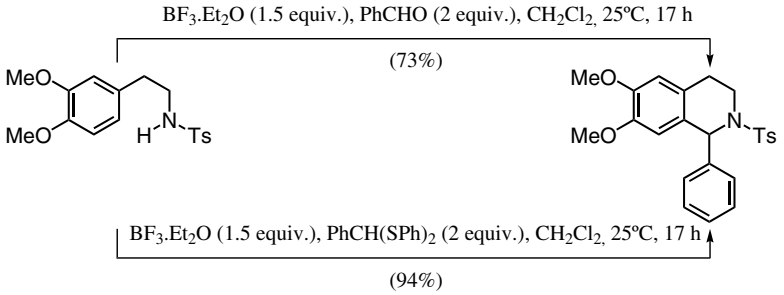
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.097

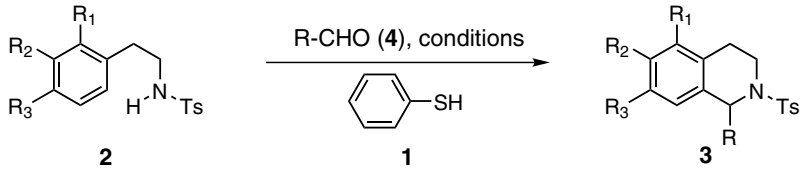


Scheme 1.

the overall transformation could be conveniently carried out as a one pot process. Herein, we report the results of our study of the effects of thiophenol (**1**) on the Pictet–Spengler condensation of *N*-sulfonyl-β-phenethylamines with aldehydes.

Four differently substituted *N*-tosyl-β-phenethylamines (**2**) and a series of 17 carbonyl compounds were employed (Table 1), including 14 mono-, di-, and tri-substituted benzaldehydes, isobutyraldehyde, and cyclohexane carboxaldehyde as non-aromatic aldehydes, and

Table 1. Effect of the addition of thiophenol (**1**) on the Pictet–Spengler synthesis of 1-substituted *N*-tosyl-1,2,3,4-tetrahydroisoquinolines (**3**)[9,10]



2 **1** **3**

Entry no.	R_1	R_2	R_3	R (aldehyde)	Solvent	Temp (°C)	Time (h)	PhSH (equiv)	Yield with additive (%)	Yield without additive (%)
1	H	OMe	OMe	C_6H_5	CH_2Cl_2	25	17	0.1	94	73
2	H	OMe	OMe	2-NO_2–C_6H_4	$ClCH_2CH_2Cl$	80	3	0.4	96	49
3	H	OMe	OMe	2-Me–C_6H_4	$ClCH_2CH_2Cl$	40	24	2.0	42	15
4	H	OMe	OMe	2-Cl–C_6H_4	CH_2Cl_2	25	8	1.0	91	19
5	H	OMe	OMe	2-Br–C_6H_4	CH_2Cl_2	25	6	1.0	86	58
6	H	OMe	OMe	2-OMe–C_6H_4	$ClCH_2CH_2Cl$	50	6	1.0	87	63
7	H	OMe	OMe	4-NO_2–C_6H_4	$ClCH_2CH_2Cl$	40	8	1.0	85	57
8	H	OMe	OMe	4-Me–C_6H_4	CH_2Cl_2	25	5	1.0	75	31
9	H	OMe	OMe	4-Cl–C_6H_4	CH_2Cl_2	25	5	1.0	84	68
10	H	OMe	OMe	4-Br–C_6H_4	CH_2Cl_2	25	8	1.0	81	63
11	H	OMe	OMe	4-OMe–C_6H_4	$ClCH_2CH_2Cl$	50	24	0.2	73	48
12	H	OMe	OMe	3-OMe–4-OH–C_6H_3	$ClCH_2CH_2Cl$	50	72	1.0	66	47
13	H	OMe	OMe	3,5-$(OMe)_2$–C_6H_3	$ClCH_2CH_2Cl$	50	3	1.0	49	31
14	H	OMe	OMe	2,4,6-$(OMe)_3$–C_6H_2	$ClCH_2CH_2Cl$	80	16	1.0	42	21
15	H	OMe	OMe	2-CF_3–C_6H_4	CH_2Cl_2	25	6	1.0	91	13
16	H	OMe	OMe	*i*-C_3H_7	CH_2Cl_2	25	3	1.0	85	48
17	H	Me	H	*i*-C_3H_7	$ClCH_2CH_2Cl$	70	8	1.0	82	43
18	H	Me	H	4-MeO–C_6H_4	$ClCH_2CH_2Cl$	80	22	1.0	71	38
19	H	Me	H	4-NO_2–C_6H_4	$ClCH_2CH_2Cl$	80	28	1.0	85	24
20	H	Me	H	2-Cl–C_6H_4	$ClCH_2CH_2Cl$	80	32	1.0	81	60
21	H	OMe	OMe	*c*-C_6H_{11}	$ClCH_2CH_2Cl$	25	1.5	1.0	88	53
22	OMe	OMe	H	4-MeO–C_6H_4	$ClCH_2CH_2Cl$	40	5	1.0	85	57
23	OMe	OMe	H	4-NO_2–C_6H_4	$ClCH_2CH_2Cl$	50	6	1.0	83	48
24	OMe	OMe	H	2-Br–C_6H_4	$ClCH_2CH_2Cl$	60	12	1.0	86	41
25	H	H	H	*i*-C_3H_7	$ClCH_2CH_2Cl$	80	48	1.0	0	0
26	H	H	H	*i*-C_3H_7	$ClCH_2CH_2Cl$	80	48	1.0[a]	0	0
27	H	OMe	OMe	Pinacolone	$ClCH_2CH_2Cl$	80	48	0.4	0	0
28	H	OMe	OMe	4-OMe–C_6H_4	$ClCH_2CH_2Cl$	50	24	1.0[b]	49	47
29	H	OMe	OMe	4-OMe–C_6H_4	$ClCH_2CH_2Cl$	80	3	1.0[c]	48	45
30	H	OMe	OMe	4-OMe–C_6H_4	$ClCH_2CH_2Cl$	50	24	1.0[d]	32	47

[a] $ZnBr_2$ (2.0 equiv) was employed.
[b] EtSH (1.0 equiv) was used in place of PhSH.
[c] ^{t}BuSH (1.0 equiv) was used in place of PhSH.
[d] MeOH (1.0 equiv) was used in place of PhSH.

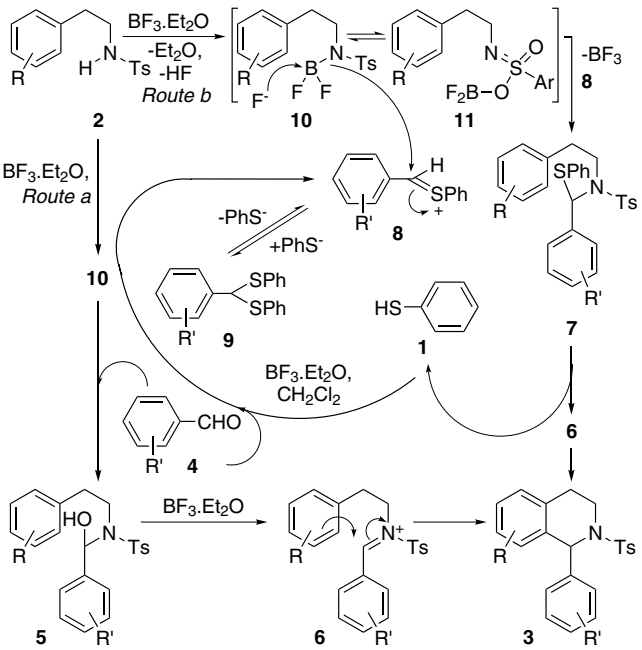
pinacolone as a test ketone. Among the substituted benzaldehydes, it was observed that the reaction showed an improvement of the product yields in the presence of thiophenol as additive. Generally, this trend was more evident when the starting aldehydes carried an *ortho* substituent than when the related *para*-substituted derivatives were employed (entries 2–6 vs 7–11).

An analogous behavior was observed when other *N*-tosyl-β-phenethylamines were employed. Noteworthy, the addition of thiophenol showed a marked increase in the cyclization leading to the trifluoromethyl derivative of entry 15, while the more activated aldehydes gave comparatively lower conversions (entries 12–14).

Yields were also influenced by the degree of activation of the aromatic moiety. When *iso*-butyraldehyde was employed, in the presence of thiophenol the activated 3,4-dimethoxy derivative provided good yields of the expected product after 3 h at room temperature (entry 16). Similar results were obtained with the less active 3-methyl derivative, after 8 h at 70 °C (entry 17); however, the less reactive *N*-sulfonyl-β-phenethylamine gave no product in refluxing 1,2-dichloroethane, even after 48 h, under either $BF_3{\cdot}Et_2O$ or $ZnBr_2$ Lewis acid promotion (entries 25 and 26). A similar trend was observed when 4-nitro- and 4-methoxy-benzaldehyde were used as carbonyl components.

The aliphatic aldehydes tested exhibited the same kind of yield improvement upon addition of thiophenol (entries 16, 17, and 21). However, not unexpectedly, the transformation did not take place with pinacolone as the carbonyl component even in the presence of the thiol (entry 27). This can be ascribed to the sterically hindered nature of this ketone and to the lower reactivity of its carbonyl group. The use of other promoters was also explored. However, ethyl mercaptan, *tert*-butyl mercaptan, and methanol were not capable of producing the reaction rate enhancement seen with thiophenol (entries 28–30).

The mechanism of the Pictet–Spengler condensation for the synthesis of THBC differs from that proposed for the production of THIQ.[11] In the latter case, it is assumed (Scheme 2, route a) that upon initial reaction of β-arylethylamine **2** with the carbonyl component **4** under Lewis acid catalysis, a hemiaminal type intermediate (**5**) is formed;[1f] next, this is converted into an iminium ion (**6**), which performs the aromatic substitution leading to the ring closed heterocycle (**3**). Formation of this iminium species is the key to the cyclization. The results of Table 1 suggest that addition of thiophenol (**1**) to the reaction medium may favor the formation of cyclized products (route b) perhaps by a three-component condensation leading to Mannich-derived *N*,*S*-acetal intermediate **7**.[12] Alternatively, generation of **7** could take place after attack of sulfonamide **2** to the sulfur-stabilized cation **8**, formed by the addition of **1** to aldehyde **4** under Lewis acid promotion (route b). However, we cannot rule out the reversible addition of thiophenol to intermediate **8**, as a possible side reaction that may lead to thioacetal **9**, which in turn could act as a



Scheme 2. The proposed mechanism for the improvement of the Pictet–Spengler cyclization reaction mediated by thiophenol.

source of key intermediate **8** en route toward **6**, through an acid-catalyzed transacetalization.[13] The nitrogen of sulfonamide **2** is non-nucleophilic and, therefore, it seems unlikely that this itself is the species attacking **8**. However, upon coordination with the Lewis acid it may undergo a loss of a proton, becoming more reactive (**10** or **11**).[14] This species would then attack **8**, with a loss of the Lewis acid, furnishing **7**. The release of **1** during the next stage could explain the improved yields observed even when sub-stoichiometric amounts of thiophenol were employed.

In light of the proposed mechanism, the different results observed when **1**, MeOH and aliphatic mercaptans were used could be ascribed to the improved ability of thiophenol to produce intermediate **6**. Perhaps this is due to an easier formation of **7**[12] (relative to production of **5** in its absence) or to the better charge stabilization capability of the phenylthio moiety (**8**), vis-à-vis its alkylthio congeners, during ion pairing with intermediate **6**. We have found an analogous behavior among thioorthoesters[7] and the group of Hevesi also noted a similar but less evident trend, while studying methyl and phenyl selenoorthoesters.[15]

In conclusion, we have demonstrated that the addition of PhSH improves the formation of tetrahydroisoquinoline products in the Pictet–Spengler cyclocondensation of *N*-sulfonyl-β-phenethylamines with aldehydes. Among the benzaldehyde derivatives, the degree of improvement is greater when the aldehyde carries an ortho substituent than when the substituent is located in the para position. This simple modification allows a convenient, more expeditious synthesis of 1-substituted tetrahydroisoquinolines.

Acknowledgments

The authors acknowledge the financial support provided by CAPES, MCT/CNPq and Fundación Antorchas. T.S.K. also thanks CONICET and ANPCyT (Project 06-12532).

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9. *Typical procedure*: To a solution of β-phenethylamine (20–30 mg) in CH_2Cl_2 or $ClCH_2CH_2Cl$ (1 mL) cooled to −20 °C under an argon atmosphere were successively added dichloromethane solutions of $BF_3{\cdot}Et_2O$ (1.5 equiv) and PhSH (0.1–2 equiv). The reaction was left to proceed under the conditions (time and temperature) shown in Table 1. Then, the reaction was quenched with brine (5 mL) and the products were extracted with EtOAc (4×20 mL); the combined extracts were washed once with brine (5 mL), dried (Na_2SO_4), concentrated under reduced pressure, and the residue was submitted to column chromatography.
10. Spectral data for selected compounds: *6,7-Dimethoxy-2-(toluene-4-sulfonyl)-1-p-tolyl-1,2,3,4-tetrahydroisoquinoline*. Mp: 121–122 °C; IR (KBr, cm^{-1}): 2934, 2835, 1611, 1519, 1464, 1337, 1247, 1159, 1018, 857, 731, and 658; ^1H NMR (200 MHz, $CDCl_3$, δ): 2.30 (s, 3H), 2.32 (s, 3H), 2.41–2.73 (m, 2H), 3.14–3.29 (m, 1H), 3.74 (s, 3H), 3.75–3.80 (m, 1H), 3.81 (s, 3H), 6.12 (s, 1H), 6.43 (s, 2H), 7.06–7.11 (m, 6H), and 7.56 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 20.89, 21.25, 26.02, 38.50, 55.72, 55.82, 58.50, 110.74, 111.17, 125.86 (2C), 126.93 (2C), 128.61 (2C), 128.76 (2C), 129.11 (2C), 137.22, 137.94, 138.50, 142.74, 147.75, and 148.07; EI-MS [*m*/*z* (%)]: 437 (M^+, 11), 346 (51), 281 (98), 280 (100), 266 (32), 191 (34), 165 (29), 91 (71), and 65 (23). Elemental analysis: Found C, 68.99; H, 6.25; N, 3.28; $C_{25}H_{27}NO_4S$ requires C, 68.62; H, 6.22; N, 3.20. *6,7-Dimethoxy-1-(2-methoxyphenyl)-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline*. Mp: 95.1–96.2 °C; IR (KBr, cm^{-1}): 2935, 2835, 1598, 1517, 1462, 1330, 1228, 1159, 1031, 975, and 657; ^1H NMR (200 MHz, $CDCl_3$, δ): 2.34 (s, 3H), 2.55–2.65 (m, 1H), 2.74–2.91 (m, 1H), 3.34–3.49 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 3.71–3.81 (m, 1H), 3.83 (s, 3H), 6.41 (s, 1H), 6.48 (s, 2H), 6.76–6.83 (m, 3H), 7.10 (d, $J = 8.2$ Hz, 2H), 7.17–7.26 (m, 1H), and 7.53 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 21.25, 26.81, 39.41, 53.41, 54.90, 55.70 (2C), 110.25, 110.57, 110.95, 119.75, 126.02, 126.92 (2C), 127.35, 128.85 (2C), 129.47, 129.91, 130.47, 138.10, 142.34, 147.43, 147.84, and 156.95; EI-MS [*m*/*z* (%)]: 453 (M^+, 10), 346 (37), 298 (100), 282 (73), 268 (41), 191 (36), 165 (52), 91 (94), and 65 (26). Elemental analysis: Found C, 66.48; H, 6.13; N, 3.27; $C_{25}H_{27}NO_5S$ requires C, 66.20; H, 6.00; N, 3.09. *6,7-Dimethoxy-2-(toluene-4-sulfonyl)-1-(2-trifluoromethyl-phenyl)-1,2,3,4-tetrahydroisoquinoline*. Mp: 106.2–107.0 °C; IR (KBr, cm^{-1}): 2935, 2854, 1612, 1517, 1454, 1348, 1247, 1161, 1037, 916, 817, 715, and 657; ^1H NMR (200 MHz, $CDCl_3$, δ): 2.34 (s, 3H), 2.64–2.70 (m, 2H), 3.43–3.61 (m, 2H), 3.66 (s, 3H), 3.79 (s, 3H), 6.35 (s, 1H), 6.44 (s, 2H), 7.13 (d, $J = 8.2$ Hz, 2H), 7.17–7.37 (m, 3H), 7.56 (d, $J = 8.2$ Hz, 2H), and 7.69–7.74 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 21.26, 26.78, 40.71, 54.84, 55.66, 55.73, 110.66, 111.08, 125.91, 126.36, 126.70, 127.32 (2C), 127.51, 128.13, 128.77, 129.13 (2C), 131.03, 131.64, 136.68, 141.22, 142.97, 147.80, and 148.10; EI-MS [*m*/*z* (%)]: 491 (M^+, 2), 346 (30), 335 (57), 266 (43), 191 (23), 176 (17), 165 (36), 91 (100), 65 (32), and 44 (63). Elemental analysis: Found C, 60.97; H, 4.95; N, 2.73; $C_{25}H_{24}F_3NO_4S$ requires C, 61.09; H, 4.92; N, 2.85. *6,7-Dimethoxy-2-(toluene-4-sulfonyl)-1-(2-bromophenyl)-1,2,3,4-tetra-hydroisoquinoline*. Mp: 59.2–60.3 °C; IR (KBr, cm^{-1}): 2951, 2934, 2834, 1611, 1516, 1464, 1348, 1250, 1162, 1025, 915, 815, 710, and 657; ^1H NMR (200 MHz, $CDCl_3$, δ): 2.35 (s, 3H), 2.76 (t, $J = 6.0$ Hz, 2H), 3.44–3.65 (m, 2H), 3.70 (s, 3H), 3.80 (s, 3H), 6.38 (s, 1H), 6.48 (s, 1H), 6.51 (s, 1H), 7.02–7.10 (m, 3H), 7.14 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.4$ Hz, 1H), and 7.68 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 21.35, 27.26, 41.00, 55.75 (2C), 58.18, 110.10, 111.05, 123.72, 125.47, 126.81, 127.35, 127.47 (2C), 128.77, 129.14 (2C), 130.50, 133.15, 136.36, 142.30, 143.00, 147.84, and 148.10; EI-MS [*m*/*z* (%)]: 501 (M^+, 4), 346 (80), 266 (93), 191 (39), 176 (29), 165 (75), 91 (100), and 65 (33).

Elemental analysis: Found C, 57.53; H, 4.72; N, 3.09; $C_{24}H_{24}BrNO_4S$ requires C, 57.37; H, 4.81; N, 2.79.

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