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Diastereoselective Passerini reactions using *p*-toluenesulfonylmethyl isocyanide (TosMIC) as the isonitrile component☆

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Abstract—*p*-Toluenesulfonylmethyl isocyanide (TosMIC) is used for the first time as the isonitrile component in a diastereoselective Passerini reaction with sugar-derived aldehydes to afford products in moderate to good yields (40–90%) and selectivities (30–90% de's).

Multi-component reactions[1] play a prominent role in synthetic organic chemistry as dependable tools for ready access to combi-libraries in short steps. Amongst these reactions, the Passerini[2] and Ugi[3] multi-component reactions occupy an important position. The Passerini reaction, which was discovered about 80 years ago, is recognized as one of the most powerful multi-component reactions with wide applications in the synthesis of diverse compounds.[4] Recently, we published[5] the *p*-toluenesulfonylmethyl isocyanide (TosMIC) mediated syntheses of *C*-oxazole and *C*-pyrrole derivatives as base surrogates, viz, *C*-nucleosides. This work motivated us to extrapolate the synthetic utility of TosMIC as an isonitrile input in a diastereoselective Passerini reaction. To the best of our knowledge, TosMIC[6] has most commonly been used in heterocyclic ring construction, in particular, of oxazole and pyrrole moieties, but less[7] in asymmetric Passerini reactions. In recent times, chiral catalyst assisted enantioselective Passerini coupling reactions have attracted much attention.[8,9] Herein, we report the first use of TosMIC as an isonitrile component in a diastereoselective Passerini reaction using sugar-derived aldehydes (Scheme 1). The advantages of using TosMIC stem from the fact that the products, besides being diversely functionalized, also bear an additional methylene group which can serve as a handle for further manipulation.

Initially, a two-component Passerini reaction (P-2CR) was performed between known[10] 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose (**1**) and TosMIC (**4**) in the presence of several Lewis acid catalysts such as $Yb(OTf)_3$ and $ZrCl_4$, however, the optimum yield of **1a** (22%, Scheme 1 and Table 1, entry 1) was obtained under Seebach's reaction conditions[11] ($TiCl_4$/TMSCl/CH_2Cl_2/0 °C-rt). Amide **1a** was identified from its spectral data, the ^1H NMR spectrum of which revealed characteristic methylene protons at δ 4.68 as a broad doublet ($J = 6.7$ Hz) and the aryl methyl at δ 2.49 as a singlet. The diastereomeric excess (de) was measured from the ^1H NMR based on the relative integration of the diastereomeric protons. For instance, **1a** revealed H-3 at δ 3.85 as a doublet for the major diastereoisomer with an integration of 0.74H and at δ 3.82 for the minor diastereoisomer with an integration of 0.26H. Likewise, the protons due to the methoxy group also resonated at different chemical shifts, that is, at δ 3.47 and δ 3.44 as singlets with the same integral ratio suggesting a de of 48%. The H-5 proton of the minor isomer resonated at δ 3.77 as a doublet ($J = 4.2$ Hz) with an integration of 0.26H while the same proton appeared at δ 3.68 as a doublet ($J = 5.0$ Hz) with an integration of 0.74H for the major diastereoisomer. The remainder of the protons resonated at their expected chemical shifts. Subsequently, the diastereoselective Passerini

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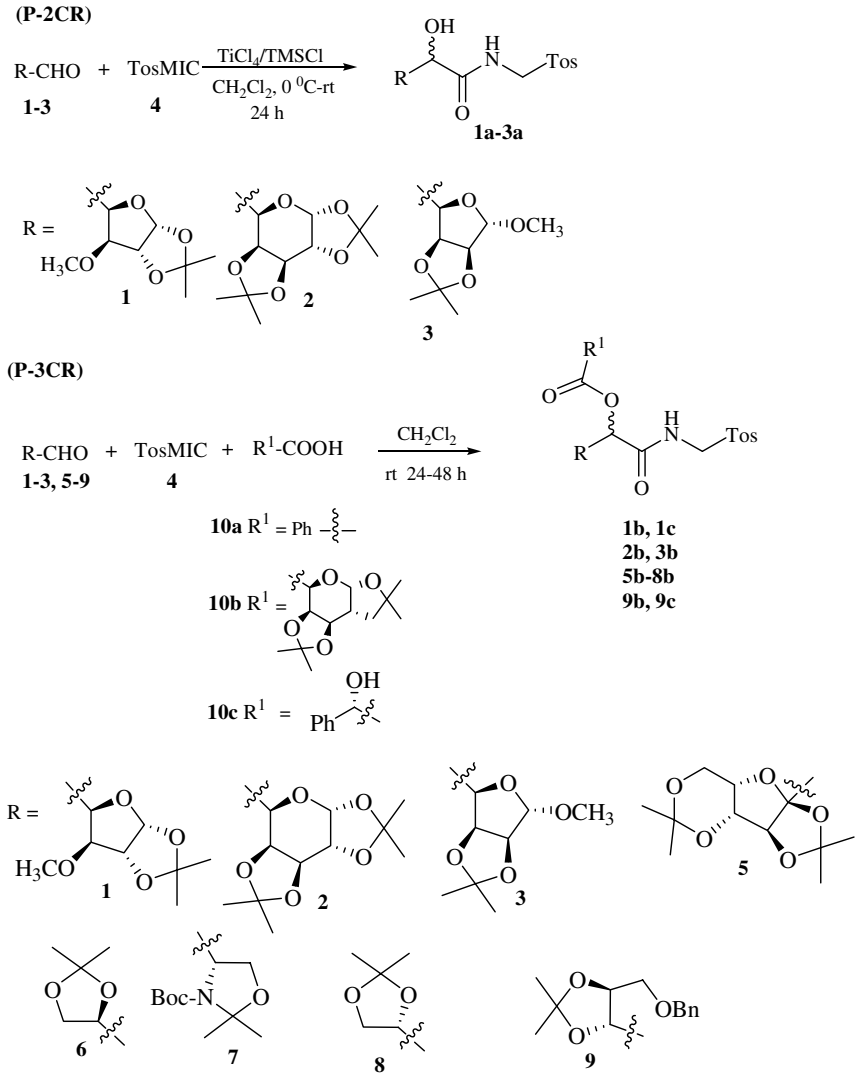

Scheme 1.

Table 1. Two-component Passerini reaction (P-2CR) of sugar-derived aldehydes with TosMIC under Lewis acid conditions[a]

Entry	Substrate	Product[b]	Yield[c]	de[d]
1	**1**	**1a**	22	48
2	**2**	**2a**	25	54
3	**3**	**3a**	59	30

[a] All the reactions were conducted as described in the general experimental procedure in the reference section.
[b] All the products were thoroughly characterized from their spectral data.
[c] Isolated yields.
[d] de calculated from the ^{1}H NMR spectra.

reaction[12] of the sugar-derived aldehydes 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose[13] **2** (Table 1, entry 2) and 1-*O*-methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,5-furanose[9] **3** (Table 1, entry 3), under the above-mentioned reaction conditions, afforded products **2a** (25%) and **3a** (59%), respectively. Analogously, the de's of **2a** and **3a** were established based on the relative integration of the diastereomeric protons in their ^{1}H NMR spectra.

Further, to establish milder reaction conditions compatible with substrates containing acid sensitive protective groups, a three-component Passerini coupling reaction (P-3CR) was performed using **1**, TosMIC **4**, and organic acids **10a–c** (PhCOOH, 1,2,3,4-di-*O*-isopropylidene-α-D-galacturonic acid[14] and mandelic acid, Table 2). However, it was found that there was no substantial enhancement in selectivity when a chiral acid **10b** was used (Table 3, entry 1). In addition, *O*-methyl-(-)-mandelic acid was also tested as an inducing agent for the Passerini reaction between aldehydes **1** and **4**; however, no product was detected under these reaction conditions. Additionally, the Passerini reaction of **1** was also attempted in the protic solvent MeOH[15] at reflux, but **1a** could only be obtained in low yield. This may be attributed to the poor stability of TosMIC under these reaction conditions.

Having established optimal reaction conditions for a mild P-3CR, several aldehydes **2**, **3**, and **5–9** when exposed to the same reaction conditions behaved uniformly to afford products **2b**, **3b**, **5b–8b**, **9b**, and

Table 2. Three-component Passerini reaction (P-3CR) between aldehyde **1**, various acids and TosMIC

Entry	Acid	Yield (%)
1	PhCOOH, **10a**	45
2	1,2,3,4-Di-*O*-isopropylidene-α-D-galacturonic acid, **10b**	35
3	(*S*)-Mandelic acid, **10c**	No reaction

Table 3. Three-component Passerini reaction (P-3CR) between sugar-derived aldehydes, organic acids and TosMIC[a]

Entry	Aldehyde	Acid(s)	Product(s)[b]	Yield[c]	de[d]
1	**1**	**10a**	**1b**	45	52
		10b	**1c**	35	50
2	**2**	**10a**	**2b**	95	28
3	**3**	**10a**	**3b**	73	35
4	**5**	**10a**	**5b**	80	69
5	**6**	**10a**	**6b**	73	28
6	**7**	**10a**	**7b**	39	90
7	**8**	**10a**	**8b**	69	25
8	**9**	**10a**	**9b**	48	41
		10b	**9c**	43	54

[a] All the reactions were conducted as described in the general experimental procedure in the reference section.
[b] All the products were thoroughly characterized by their spectral data.
[c] Isolated yields.
[d] de calculated from ^{1}H NMR spectra.

9c, respectively (Table 3). Particular mention needs to be made about 1,2-*O*-isopropylidene-(*R*)-glyceraldehyde **6**, a reluctant substrate under Lewis acid conditions, however, which underwent a facile three-component Passerini reaction to afford **6b** in 73% yield and 28% de (Table 3, entry 5). The diastereomeric excess of all the products was established by ^{1}H NMR analysis. For instance, the ^{1}H NMR spectrum of **1b** displayed the characteristic H-1 signal at δ 5.98 as a doublet ($J = 3.7$ Hz) for the major diastereoisomer while the same proton appeared at δ 5.87 for the minor diastereoisomer with an integral ratio of 3.16:1.0 (de 52%). H-5 appeared at δ 5.50 and at δ 5.28 for the minor and major diastereoisomers, respectively, with the same integral ratio, while the remainder of the protons appeared at their expected chemical shifts. The major isomer of **1b** {mp = 179 °C; $[\alpha]_D$ −61.03 (*c* 0.25, $CHCl_3$)} was also isolated as a single diastereoisomer whose ^{1}H NMR revealed H-1 at δ 5.96 as a doublet ($J = 3.0$ Hz) and the characteristic H-5 proton at δ 5.29 as a doublet ($J = 9.1$ Hz) with the rest of the protons resonating at their expected chemical shifts. The absolute stereochemistry at the newly created carbon in **1b** was assigned as '*R*' (major isomer, L-ido) based on the coupling constant ($J_{5,4} = 9.1$ Hz). By analogy, the stereochemistry at the newly created center for the major diastereoisomers of **2b** and **3b** was assigned as '*R*' since the starting aldehydes were drawn from D-sugars. Similarly, the de values of all the other products (**5b**–**8b**, **9b** and **9c**) were calculated based on the integrations of the diastereomeric protons and the stereochemistry at the newly created center (major isomer) was assigned as being *anti* to the existing center.[16]

In summary, TosMIC was introduced for the first time as a novel isonitrile component in diastereoselective Passerini reactions. Several sugar-derived aldehydes were compatible under these reaction conditions to afford diverse products as mandelamides[17,18] in moderate to good yields and in moderate to good selectivities.

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17. *General P-2CR experimental procedure (Lewis acid conditions)*: To a stirred solution of $TiCl_4$ (0.3 mmol) and aldehyde (1.0 mmol) in CH_2Cl_2 (5 mL) was added trimethyl chlorosilane at 0 °C and then TosMIC (1.05 mmol) was added. The reaction mixture was warmed to room temperature, and stirred for about 24 h. After completion, the reaction was quenched with saturated aq $NaHCO_3$ solution (5 mL), the organic layer separated and the

aqueous phase extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and purified by column chromatography (silica gel 60–120 mesh, EtOAc: *n*-hexane, 8:2) to afford products **1a**–**3a** in 22–59% yields.

General P-3CR experimental procedure (PhCOOH conditions): In a round-bottomed flask, aldehyde (0.52 mmol) was dissolved in CH_2Cl_2 (2.5 mL). To this solution were added benzoic acid (0.52 mmol) and TosMIC (0.45 mmol) and the resulting mixture stirred for 24–48 h. After complete consumption of TosMIC, 1 M HCl solution (3 mL) was added to denature excess TosMIC. The reaction was diluted with water (5 mL), extracted with CH_2Cl_2 (2×10 mL), the combined organic layers dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (silica gel 60–120 mesh, EtOAc: *n*-hexane, 1:1) to give **1b**, **1c**, **2b**, **3b**, **5b**–**8b**, **9b**, and **9c** in 35–95% yields.

18. *Spectral data for selected compounds*. Compound **1a**: pale yellow liquid; $[\alpha]_D$ −15.07 (*c* 0.25, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (m, 2H, Ar–H), 7.50 (t, 1H, $J = 5.8$ Hz, NH), 7.35 (d, 2H, $J = 7.56$ Hz, Ar–H), 5.95 (d, 1H, $J = 3.3$ Hz, H-1), 4.68 (br d, 2H, $J = 6.7$ Hz, CH_2) 4.55 (d, 1H, $J = 4.2$ Hz, H-2), 4.24–4.14 (m, 1H, H-4), 3.85 (d, 0.74H, $J = 2.5$ Hz, H-3), 3.82 (d, 0.26H, $J = 3.3$ Hz, H-3), 3.77 (d, 0.26H, $J = 4.2$ Hz, H-5), 3.68 (d, 0.74H, $J = 5.0$ Hz, H-5) 3.47 (s, 2.22H, OMe), 3.44 (s, 0.78H, OMe), 2.49 (s, 3H, Ar–CH_3), 1.50 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); IR (KBr): 3346, 2990, 1693, 1597, 1288, 1085 cm^{-1}; FABMS: (*m*/*z*) (%): 416 (M+1, 10); Anal. Calcd for $C_{18}H_{25}NO_8S$: C, 52.04; H, 6.07%. Found: C, 52.10; H, 6.09%; Compound **1b**: yellow solid; mp = 179 °C; $[\alpha]_D$ +1.36 (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.17–7.99 (m, 2H, Ar–H), 7.79–7.68 (m, 2H, Ar–H), 7.61–7.38 (m, 3H, Ar–H and NH), 7.32–7.14 (m, 3H, Ar–H), 5.98 (d, 0.76H, $J = 3.7$ Hz, H-1), 5.87 (d, 0.24H, $J = 3.7$ Hz, H-1), 5.50 (d, 0.24H, $J = 6.6$ Hz, H-5), 5.28 (d, 0.76H, $J = 8.9$ Hz, H-5), 4.70–4.42 (m, 4H, CH_2, H-2 and H-4), 3.83–3.77 (t, 1H, $J = 3.7$ Hz, H-3), 3.31 (s, 0.72H, OMe), 3.27 (s, 2.28H, OMe), 2.37 (s, 3H, Ar–CH_3), 1.55 (s, 2.28H, CH_3), 1.50 (s, 0.72H, CH_3), 1.34 (s, 2.28H, CH_3), 1.31 (s, 0.72H, CH_3); IR (KBr): 3344, 2931, 1722, 1599, 1321, 1287 cm^{-1}; FABMS: *m*/*z* (%): 520 (M^++1, 5); Anal. Calcd for $C_{25}H_{29}NO_9S$: C, 57.79; H, 5.63%. Found: C, 57.80; H, 5.59%; Compound **1b** (major): yellow solid; mp = 179 °C; $[\alpha]_D$ −61.03 (*c* 0.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, 2H, $J = 7.5$ Hz, Ar–H), 7.76 (d, 2H, $J = 8.3$ Hz, Ar–H), 7.56 (t, 1H, $J = 7.5$ Hz, Ar–H), 7.42 (t, 2H, $J = 8.3$ Hz, Ar–H), 7.25 (d, 2H, $J = 8.3$ Hz, Ar–H), 7.06 (t, 1H, $J = 6.7$ Hz, NH), 5.96 (d, 1H, $J = 3.0$ Hz, H-1), 5.29 (d, 1H, $J = 9.1$ Hz, H-5), 4.62 (d, 2H, $J = 6.7$ Hz, CH_2), 4.55 (d, 1H, $J = 3.0$ Hz, H-2), 4.46 (dd, 1H, $J = 9.1$, 3.0 Hz, H-4), 3.78 (d, 1H,$J = 3.7$ Hz, H-3), 3.29 (s, 3H, OMe), 2.36 (s, 3H, Ar–CH_3), 1.53 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); Anal. Calcd for $C_{25}H_{29}NO_9S$: C, 57.79; H, 5.63%. Found: C, 57.77; H, 5.62%; Compound **2a**: pale yellow liquid; $[\alpha]_D$ −61.03 (*c* 0.25, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, 2H, $J = 7.9$ Hz, Ar–H), 7.64 (t, 0.77H, $J = 7.2$ Hz, NH), 7.53 (t, 0.23H, $J = 5.8$ Hz, NH), 7.30 (d, 2H, $J = 7.9$ Hz, Ar–H), 5.56 (d, 0.77H, $J = 5.1$ Hz, H-1), 5.43 (d, 0.23H, $J = 5.1$ Hz, H-1), 4.80 (m, 2H, CH_2), 4.62–4.00 (m, 4H), 3.90 (dd, 1H, $J = 1.45$, 7.27 Hz, H-5), 3.70 (br s, 1H, OH), 2.45 (s, 3H, Ar–CH_3), 1.60–1.19 (m, 12H, $4 \times CH_3$); IR (neat): 3449, 2987, 1689, 1599, 1381, 1255 cm^{-1}; ES–MS: *m*/*z* (%): 472 (M^++1, 68); Anal. Calcd for $C_{21}H_{29}NO_9S$: C, 53.49; H, 6.20%. Found: C, 53.50; H, 6.19%; Compound **7b**: white solid; mp = 75–76 °C; $[\alpha]_D$ −7.72 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–8.01 (m, 3H, Ar–H), 7.68–7.64 (m, 2H, Ar–H), 7.58–7.50 (m, 1H, NH), 7.44–7.35 (m, 2H, Ar–H), 7.20 (d, 2H, $J = 7.2$ Hz, Ar–H), 5.29 (d, 1H, $J = 7.9$ Hz, CH), 4.67–4.57 (br s, 2H, CH_2), 4.39–4.24 (m, 1H, CH), 4.02–3.97 (d, 1H, $J = 9.4$ Hz, CH), 3.90–3.79 (m, 1H, CH) 2.40 (s, 0.15H, Ar–CH_3), 2.36 (s, 2.85H, Ar–CH_3) 1.46–1.24 (m, 15H); IR (KBr): 3386, 2980, 1701, 1599, 1321, 1146, 1104 cm^{-1}; ES–MS: *m*/*z* (%): 548 (M^++2, 100); Anal. Calcd for $C_{27}H_{34}N_2O_8S$: C, 59.32; H, 6.27%. Found: C, 59.30; H, 6.30%.