Efficient Synthesis of Racemic α-Aryl-α-amino Acid Esters via Aminoalkylation with in situ Generated Glycine Cation Equivalents

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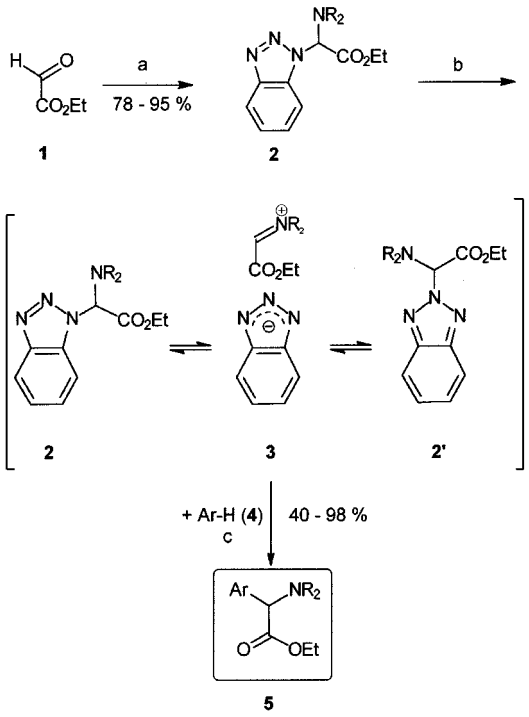
Abstract: Iminium salts generated in situ from ethyl glyoxylate, secondary amines and 1-*H*-benzotriazole are demonstrated to be excellent reagents for the regioselective mono-aminoalkylation of indoles, phenols, furans and pyrroles. This method provides a simple and straightforward "one-pot" reaction sequence to a variety of ethyl α-aryl-α-amino acid esters **5** and **8** in high yields.

Key words: α-aryl-α-amino acids, ternary iminium salt, aminoalkylation, Mannich reaction, glycine cation equivalents

Nonproteinogenic α-aryl-α-amino acids are interesting building blocks in the synthesis of natural products and, in general, of biologically active compounds.[1] The classical Mannich procedure is only suitable for the formation of a few α-aryl-α-amino acids derived from very electron-rich aromatic compounds.[2,3] Therefore, several synthetic routes to this attractive class of substances have been developed.[1a,1h,4] Numerous synthetic routes starting from O'Donnell's Schiff bases[1f,5] or arylglyoxylates[1g,6,7] are convenient methods for the synthesis of arylglycines. However, these methods in general require tedious multistep procedures. Furthermore, they are often restricted to only few types of arenes or the yields are quite poor.[8] The method of Heaney[9] for the preparation of α-aryl-α-amino acids leads to good yields. However, long reaction times, limitation to very electron-rich aromatic heterocycles and the difficult preparation of the *N*,*O*-acetals[10] are the main restrictions of this strategy. Our motivation to use glycine cation equivalents in the manner of reactive ternary iminium salts for the aminoalkylation of numerous nucleophilic aromatic compounds is the consequence of the latest developments in modern variants of the Mannich reaction.[11] Recently, we have disclosed that the aminoalkylation of electron-rich aromatic compounds with ternary iminium salts (containing alkyl and aryl groups) provides the corresponding Mannich products in good to excellent yields.[12] Our current goal is the development of an efficient and inexpensive synthetic route using readily available starting materials to yield aromatic α-amino acids in a simple "one-pot" reaction sequence.

Some preliminary studies of Groß[13] and Katritzky[14,15] have been very helpful for our purposes. Groß et al.[13] have described a facile method for the formation of aromatic α-amino carboxylates. However, this method was not pursued further, may be due to the difficult preparation[10,16] and handling of the described iminium salt. A better preparation and simple handling of the ternary iminium salts derived from alkyl glyoxylates are the requirements for the efficient aminoalkylation of aromatic compounds.

Here we describe the in situ generation of the ternary iminium salts **3a–d** as glycine cation equivalents from easily accessible substituted ethyl glyoxylate aminals **2a–d**. The aminals are derived according to Katritzky[14] from com-



2, 3	R_2
a	]-$(CH_2)_5$-[
b	]-$(CH_2)_2$-O-$(CH_2)_2$-[
c	(-CH_2-CH=CH_2)$_2$
d	(-CH_2-Ph)$_2$

4	Ar-H
a	2-naphthol
b	resorcinol
c	resorcinol momomethyl ether
d	resorcinol dimethyl ether
e	4-methyl-phenol
f	3-methyl-phenol
g	2-methylfuran
h	*N*-methylindole
i	*N*-methylpyrrole
j	*N*,*N*-dimethylaniline

Reagents and conditions: a) Bt-H/HNR_2/Toluene, 65°C, 5 h; b) Lewis acid/THF or CH_2Cl_2, 1 h; c) THF or CH_2Cl_2

Scheme 1

mercially available ethyl glyoxylate (**1**),[17] 1-*H*-benzotriazole (Bt-H)[18] and a secondary amine (Scheme 1, Table 1). The benzotriazol-2-yl isomers (**2'**) in the equilibrium mixtures of both the benzotriazol-1-yl (**2**) and **2'** isomers[19] have no detrimental influence on the aminoalkylation reaction. ^{1}H NMR data of $CDCl_3$ solutions of **2** exhibit, in all cases, two singlets in the region 6.10 – 6.50 ppm, corresponding to the NC*H*N proton, indicating the presence of both **2** and **2'** isomers (ratio **2**:**2'** = 85:15 to 80:20).[20] Changing the solvent resulted in different ratios of the benzotriazol-1-yl and -2-yl isomers.[21]

The iminium salts **3** are generated in situ by an electrophilic attack of a Lewis acid on the aminals **2**. The following nucleophilic attack of **4** on the iminium salt **3** yields the ethyl α-aryl-α-amino carboxylates **5** (Scheme 1).

We started our studies using 2-naphthol (**4a**) and *N*-methylindole (**4h**) owing to the fact that these nucleophilic aromatic compounds are standards in aminoalkylation reactions.[12,22] With reference to O'Donnell[5c] and Gilchrist et al.,[23] the experiments were conducted to find the best conditions in terms of Lewis acid, solvent, temperature and stoichiometry. $AlCl_3$ in THF (reflux; Method A) for aminoalkylation of **4a–g** and $TiCl_4$ in dichloromethane at –78°C (Method B) for **4h–j** gave the highest yields. These procedures were also employed successfully for the aminoalkylation of considerably less active aromatic compounds **4e–g**, **4i** and **4j**. In comparison, this one-pot procedure requires mild reaction conditions.

When more powerful Lewis acids were used, such as Me_3SiOTf (Tf = CF_3SO_2) and $Me_3SiB(OTf)_4$,[24] a black, semi-solid product resulted. The use of $FeCl_3$, $ZnCl_2$, $ZnBr_2$ or an excess of Lewis acid led to poorer yields. The ethyl α-aryl-α-amino carboxylates **5** were isolated by quenching the reaction mixture with aqueous $NaHCO_3$ followed by the usual workup (2 N NaOH; extraction with dichloromethane) and crystallization or purification by chromatography on silica gel. The ethyl α-aryl-α-amino carboxylates **5c, 5f–j, 5n** and **5p** (Table 2) can be used without further purification.

In all experiments with phenols as aromatic substrates **4**, we observed a regioselective *ortho*-aminoalkylation of these derivatives with respect to the hydroxy group. The results are summarized in Table 2. In contrast to Heaney's[25] earlier studies of Friedel–Crafts alkylation reactions of electron-rich aromatic compounds, the aminoalkylation of *N*-methylindole (**4h**) always led to the expected 3-monoaminoalkylated products in high yields. The interaction of the iminium salts **3c** or **3d** with $TiCl_4$ and **4h** in dichloromethane (–40°C; 3–6 h) gave the di-indolylacetate (**6**).[25,26]

The ethyl α-aryl-α-amino carboxylates **5** can be saponified to α-aryl-α-amino acids **7** by treating them with 6 N NaOH in the presence of some 1,4-dioxane (room temper-

Table 1 Ethyl Glyoxylate Aminals **2** Prepared

Product[a]	mp (°C) or Appearance	NR_2	Yield[b] (%)	^{1}H NMR (200 MHz, $CDCl_3$/TMS)[c] δ, J (Hz)	IR (KBr or film) ν (cm^{-1})
2a	83–84[d]	1-piperidin-1-yl	86[d]	1.23 (t, 3 H, J = 7.1, CH_2CH_3), 1.32–1.42 [m, 2 H, $N(CH_2)_5$], 1.59–1.69 [m, 4 H, $N(CH_2)_5$], 2.49–2.77 (m, 4 H, CH_2NCH_2), 4.28 (dq, 2 H, J = 7.1, 2.3, CH_2CH_3), 6.17 (s, 1 H, NCHN), 7.34–7.53 (m, 2 H, ArH), 7.69 (d, 1 H, J = 8.3, ArH), 8.09 (d, 1 H, J = 8.2, ArH)	2939, 2930, 2814, 1763, 1449, 1235, 1191, 1181, 1125, 1081, 1027, 753, 744
2b	yellow oil	1-morpholin-1-yl	86	1.21 (t, 3 H, J = 7.1, CH_2CH_3), 2.58–2.83 (m, 4 H, CH_2NCH_2), 3.66–3.83 (m, 4 H, CH_2OCH_2), 4.27 (q, 2 H, J = 7.1, CH_2CH_3), 6.16 (s, 1 H, NCHN), 7.31–7.56 (m, 2 H, ArH), 7.73 (d, 1 H, J = 8.3, ArH), 8.09 (d, 1 H, J = 7.9, ArH)	2969, 2857, 1749, 1451, 1265, 1218, 1177, 1123, 1069, 1029, 749
2c	yellow oil	$(allyl)_2N$	96	1.22 (t, 3 H, J = 7.1, CH_2CH_3), 3.05–3.19 [m, 2 H, $N(CH_2CH{=}CH_2)_2$], 3.61–3.73 [m, 2 H, $N(CH_2CH{=}CH_2)_2$], 4.27 (dq, 2 H, J = 7.1, 1.0, CH_2CH_3), 5.16–5.32 [m, 4 H, $N(CH_2CH{=}CH_2)_2$], 5.72–5.93 [m, 2 H, $N(CH_2CH{=}CH_2)_2$], 6.35 (s, 1 H, NCHN), 7.29–7.65 (m, 3 H, ArH), 8.09 (d, 1 H, J = 8.2, ArH)	3092, 2981, 1751, 1450, 1370, 1277, 1260, 1215, 1179, 1132, 1108, 1060, 1029, 1002, 928, 747
2d	yellow oil	Bn_2N	95	1.22 (t, 3 H, J = 7.1, CH_2CH_3), 3.41 (d, 2 H, J = 13.9, NCH_2Ph), 4.19–4.37 (m, 4 H, CH_2CH_3, NCH_2Ph), 6.20 (s, 1 H, NCHN), 7.14–7.50 (m, 13 H, ArH), 8.13 (d, 1 H, J = 8.6, ArH)	3082, 3030, 2982, 1752, 1494, 1452, 1370, 1217, 1154, 1075, 1060, 1027, 745, 699

[a] Satisfactory microanalyses obtained C ± 0.4, H ± 0.3, N ± 0.3.
[b] Yields of isolated products.
[c] ^{1}H NMR data are given for the major benzotriazol-1-yl isomers **2a–d**.
[d] Lit[14] yield: 78%, mp 84–85 °C.

Table 2 Aminoalkylation of Aromatic Compounds **4** Using in situ Generated Ternary Iminium Salts **3**

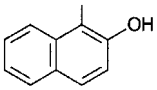
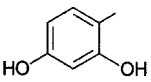
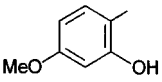
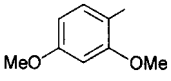
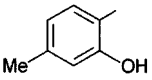
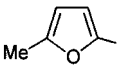
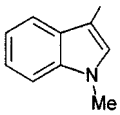
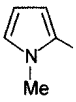
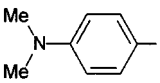
Product[a]	mp (°C)	NR_2	Ar- (**4**)	Method	Yield[b] (%)	^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	IR (KBr or film) ν (cm^{-1})
5a	72–73	1-piperidin-1-yl		A	87	1.12 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.52–1.71 [m, 6 H, $N(CH_2)_5$], 2.38–2.42 (m, 4 H, CH_2NCH_2), 4.09 (dq, 2 H, *J* = 7.1, 1.6, CH_2CH_3), 4.83 (s, 1 H, ArCHN), 7.08 (d, 1 H, *J* = 8.9, ArH), 7.25–7.33 (m, 1 H, ArH), 7.42–7.51 (m, 1 H, ArH), 7.66–7.75 (m, 2 H, ArH), 8.01 (d, 1 H, *J* = 8.6, ArH), 12.01 (br s, 1 H, ArO*H*)	2954, 2938, 2818, 1742, 1622, 1600, 1473, 1373, 1366, 1330, 1303, 1273, 1240, 1227, 1177, 1159, 1144, 1110, 1018, 831, 750
5b	red oil	1-piperidin-1-yl		A	83[c]	1.24 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.52–1.65 [m, 6 H, $N(CH_2)_5$], 2.54–2.57 (m, 4 H, CH_2NCH_2), 4.06 (s, 1 H, ArCHN), 4.18 (q, 2 H, *J* = 7.1, CH_2CH_3), 6.30–6.42 (m, 2 H, ArH), 6.86 (d, 1 H, *J* = 8.2, ArH), 7.85 (br s, 1 H, ArOH)	3358, 2935, 2854, 1742, 1626, 1601, 1516, 1467, 1454, 1313, 1220, 1173, 1112, 1026, 976
5c	yellow oil	1-piperidin-1-yl		A	70	1.24 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.51–1.72 [m, 6 H, $N(CH_2)_5$], 2.54–2.58 (m, 4 H, CH_2NCH_2), 3.76 (s, 3 H, OCH_3), 4.07 (s, 1 H, ArCHN), 4.12–4.30 (m, 2 H, CH_2CH_3), 6.22–6.50 (m, 2 H, ArH), 6.91 (d, 1 H, *J* = 8.4, ArH)	2936, 2853, 1744, 1625, 1588, 1511, 1454, 1220, 1202, 1183, 1111, 1033
5d	yellow oil	1-piperidin-1-yl		A	76[c]	1.20 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.40–1.68 [m, 6 H, $N(CH_2)_5$], 2.41–2.48 (m, 4 H, CH_2NCH_2), 3.79 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.01–4.27 (m, 2 H, CH_2CH_3), 4.46 (s, 1 H, ArCHN), 6.38–6.54 (m, 2 H, ArH), 7.39 (d, 1 H, *J* = 8.3, ArH)	2934, 1737, 1611, 1587, 1505, 1464, 1454, 1296, 1257, 1208, 1157, 1107, 1034, 826
5e	yellow oil	1-piperidin-1-yl		A	53[c]	1.26 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.52–1.74 [m, 6 H, $N(CH_2)_5$], 2.30 (s, 3 H, $ArCH_3$), 2.45–2.68 (m, 4 H, CH_2NCH_2), 4.12 (s, 1 H, ArCHN), 4.20 (q, 2 H, *J* = 7.1, CH_2CH_3), 6.60–6.70 (m, 2 H, ArH), 6.92 (d, 1 H, *J* = 7.7, ArH), 11.18 (br s, 1 H, ArO*H*)	2935, 2854, 1744, 1628, 1581, 1453, 1369, 1266, 1220, 1187, 1155, 1118, 1028, 804
5f	yellow oil	1-piperidin-1-yl		A	86	1.26 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.36–1.48 [m, 2 H, $N(CH_2)_5$], 1.57–1.68 [m, 4 H, $N(CH_2)_5$], 2.28 (s, 3 H, $ArCH_3$), 2.36–2.57 (m, 4 H, CH_2NCH_2), 4.16–4.30 (m, 3 H, ArCHN, CH_2CH_3), 5.91–5.93 (m, 1 H, ArH), 6.22-6.24 (m, 1 H, ArH)	3418, 2940, 2856, 2378, 2348, 1743, 1633, 1452, 1368, 1228, 1202, 1159, 1116, 1026, 789, 748
5g	yellow oil	1-piperidin-1-yl		B[d]	98	1.22 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.31–1.63 [m, 6 H, $N(CH_2)_5$], 2.38–2.60 (m, 4 H, CH_2NCH_2), 3.73 (s, 3 H, NCH_3), 4.06–4.26 (m, 2 H, CH_2CH_3), 4.36 (s, 1 H, ArCHN), 6.97–7.29 (m, 4 H, ArH), 7.80 (d, 1 H, *J* = 7.7, ArH)	3419, 2932, 2852, 2359, 1731, 1633, 1469, 1372, 1332, 1152, 1118, 1032, 741
5h	yellow oil	1-piperidin-1-yl		B[d]	89	1.26 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.35–1.63 [m, 6 H, $N(CH_2)_5$], 2.37–2.56 (m, 4 H, CH_2NCH_2), 3.70 (s, 3 H, N-CH_3), 4.06–4.22 (m, 2 H, CH_2CH_3), 4.26 (s, 1 H, ArCHN), 6.02–6.06 (m, 1 H, ArH), 6.09–6.19 (m, 1 H, ArH), 6.58–6.64 (m, 1 H, ArH)	2933, 2852, 2352, 2339, 1745, 1443, 1310, 1297, 1180, 1155, 1118, 1030, 712
5i	yellow oil	1-piperidin-1-yl		B[e]	72	1.22 (t, 3 H, *J* = 7.1, CH_2CH_3), 1.42–1.46 (m, 2 H, $N(CH_2)_5$], 1.57–1.71 [m, 4 H, $N(CH_2)_5$], 2.29–2.48 (m, 4 H, CH_2NCH_2), 2.95 [s, 6 H, $N(CH_3)_2$], 3.84 (s, 1 H, ArCHN), 4.02–4.29 (m, 2 H, CH_2CH_3), 6.69 (d, 1 H, *J* = 8.6, ArH), 7.30 (d, 1 H, *J* = 8.6, ArH)	2932, 2850, 2801, 1741, 1612, 1526, 1444, 1350, 1223, 1162, 1115, 1030, 946, 823

Table 2 (continued)

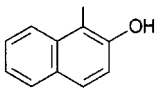
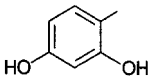
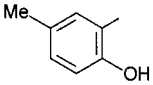
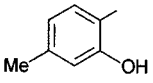
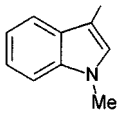
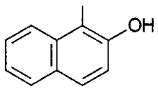
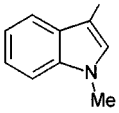
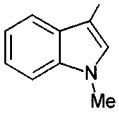
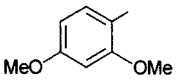
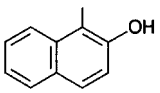
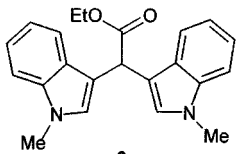
Product[a]	mp (°C)	NR_2	Ar- (**4**)	Method	Yield[b] (%)	^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	IR (KBr or film) ν (cm^{-1})
5j	yellow oil	1-morpholin-1-yl		A	85	1.11 (t, 3 H, *J* = 7.1, CH_2CH_3), 2.56–2.79 (m, 4 H, CH_2NCH_2), 3.79–3.84 (m, 4 H, CH_2OCH_2), 3.97–4.23 (m, 2 H, CH_2CH_3), 4.88 (s, 1 H, ArCHN), 7.06–7.11 (m, 1 H, ArH), 7.25–7.35 (m, 1 H, ArH), 7.41–7.54 (m, 1 H, ArH), 7.69–7.77 (m, 2 H, ArH), 8.03 (d, 1 H, *J* = 8.6, ArH), 11.28 (br s, 1 H, ArO*H*)	2961, 2917, 2854, 2353, 2339, 1736, 1622, 1600, 1469, 1455, 1370, 1266, 1186, 1121, 1030, 748
5k	red oil	1-morpholin-1-yl		A	77[c]	1.22 (t, 3 H, *J* = 7.1, CH_2CH_3), 2.48–2.70 (m, 4 H, CH_2NCH_2), 3.72–3.94 (m, 4 H, CH_2OCH_2), 4.03 (s, 1 H, ArCHN), 4.09–4.30 (m, 2 H, CH_2CH_3), 6.29–6.56 (m, 2 H, ArH), 6.92 (d, 1 H, *J* = 8.3, ArH), 9.06 (br s, 2 H, ArO*H*)	3262, 2960, 2925, 2856, 1734, 1623, 1602, 1517, 1455, 1384, 1313, 1267, 1195, 1174, 1158, 1119, 1070, 1030, 975, 748
5l	yellow oil	1-morpholin-1-yl		A	40[c]	1.23 (t, 3 H, *J* = 7.1, CH_2CH_3), 2.24 (s, 3 H, $ArCH_3$), 2.57–2.68 (m, 4 H, CH_2NCH_2), 3.75–3.80 (m, 4 H, CH_2OCH_2), 4.04 (s, 1 H, ArCHN), 4.10–4.31 (m, 2 H, CH_2CH_3), 6.74 (d, 1 H, *J* = 8.2, ArH), 6.87 (s, 1 H, ArH), 6.98–7.04 (m, 1 H, ArH), 9.76 (br s, 1 H, ArO*H*)	3389, 2959, 2920, 2855, 2352, 2347, 1737, 1633, 1500, 1454, 1384, 1267, 1185, 1148, 1118, 1030, 899, 749
5m	yellow oil	1-morpholin-1-yl		A	43[c]	1.11 (t, 3 H, *J* = 7.1, CH_2CH_3), 2.16 (s, 3 H, $ArCH_3$), 2.46–2.52 (m, 4 H, CH_2NCH_2), 3.57–3.69 (m, 4 H, CH_2OCH_2), 3.95 (s, 1 H, ArCHN), 3.97–4.14 (m 2 H, CH_2CH_3), 6.50–6.57 (m, 2 H, ArH), 6.84 (d, 1 H, *J* = 7.6, ArH), 9.77 (br s, 1 H, ArO*H*)	3390, 2955, 2921, 2854, 1741, 1627, 1580, 1453, 1270, 1194, 1157, 1117, 1030, 891
5n	yellow oil	1-morpholin-1-yl		B[d]	93	1.23 (dt, 3 H, *J* = 7.1, 1.1, CH_2CH_3), 2.44–2.65 (m, 4 H, CH_2NCH_2), 3.58 –3.85 (m, 7 H, NCH_3, CH_2OCH_2), 4.04–4.28 (m, 2 H, CH_2CH_3), 4.37 (s, 1 H, ArCHN), 7.06–7.42 (m, 4 H, ArH), 7.84 (d, 1 H, *J* = 7.6, ArH)	3448, 2958, 2855, 1737, 1473, 1372, 1331, 1246, 1183, 1153, 1134, 1116, 1032, 735
5o	yellow oil	$(allyl)_2N$		A	74[f]	1.10 (t, 3 H, *J* = 7.1, CH_2CH_3), 3.24–3.49 [m, 4 H, $N(CH_2CH{=}CH_2)_2$], 3.94–4.27 (m, 2 H, CH_2CH_3), 5.09 (s, 1 H, ArCHN), 5.17–5.28 [m, 4 H, $N(CH_2CH{=}CH_2)_2$], 5.81–6.07 [m, 2 H, $N(CH_2CH{=}CH_2)_2$], 7.10 (d, 2 H, *J* = 8.9, ArH), 7.24–7.32 (m, 1 H, ArH), 7.42–7.51 (m, 1 H, ArH), 7.67–7.75 (m, 2 H, ArH), 8.00 (d, 1 H, *J* = 8.6, ArH), 11.50 (br s, 1 H, ArO*H*)	2980, 1737, 1622, 1601, 1468, 1454, 1368, 1270, 1246, 1235, 1184, 1161, 1143, 1111, 1027, 997, 929, 825, 747
5p	yellow oil	$(allyl)_2N$		B[g]	96	1.25 (t, 3 H, *J* = 7.1, CH_2CH_3), 3.16–3.40 [m, 4 H, $N(CH_2CH{=}CH_2)_2$], 3.70 (s, 3 H, NCH_3), 4.04–4.33 (m, 2 H, CH_2CH_3), 4.92 (s, 1 H, ArCHN), 5.06–5.21 [m, 4 H, $N(CH_2CH{=}CH_2)_2$], 5.74–6.03 [m, 2 H, $N(CH_2CH{=}CH_2)_2$], 6.95–7.29 (m, 4 H, ArH), 7.10–7.85 (m, 1 H, ArH)	2977, 2956, 2926, 1742, 1468, 1445, 1373, 1332, 1179, 1153, 1120, 919, 746
5q	92	Bn_2N		B[h]	84[i]	1.31 (t, 3 H, *J* = 7.1, CH_2CH_3), 3.55–3.79 (m, 5 H, NCH_3, $N(CH_2Ph)$), 3.84–3.97 (m, 2 H, $N(CH_2Ph)$), 4.08–4.43 (m, 2 H, CH_2CH_3), 4.88 (s, 1 H, ArCHN), 6.97–7.41 (m, 14 H, ArH), 7.49–7.60 (m, 1 H, ArH)	3069, 3029, 2974, 2937, 2833, 2815, 1724, 1495, 1474, 1453, 1336, 1173, 1153, 1138, 1033, 999, 751, 697
5r	yellow oil	Bn_2N		A	79[j]	1.24 (t, 3 H, *J* = 7.1 , CH_2CH_3), 3.63–3.91 [m, 10 H, 2 OCH_3, $N(CH_2Ph)_2$], 4.06–4.32 (m, 2 H, CH_2CH_3), 4.74 (s, 1 H, ArCHN), 6.34–6.57 (m, 2 H, ArH), 7.03–7.49 (m, 11 H, ArH)	2935, 2837, 1732, 1612, 1586, 1505, 1454, 1296, 1218, 1159, 1133, 1031, 835, 747, 699

Table 2 (continued)

Product[a]	mp (°C)	NR_2	Ar- (**4**)	Method	Yield[b] (%)	^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	IR (KBr or film) ν (cm^{-1})
5s	yellow oil	Bn_2N		A	81[i]	1.13 (t, 3 H, *J* = 7.1, CH_2CH_3), 3.86 [s, 4 H, $N(CH_2Ph)_2$], 3.96–4.24 (m, 2 H, CH_2CH_3), 5.28 (s, 1 H, ArCHN), 7.21–7.61 (m, 13 H, ArH), 7.80–7.87 (m, 2 H, ArH), 8.00 (d, 1 H, *J* = 8.5, ArH), 11.93 (br s, 1 H, ArO*H*)	3062, 3030, 2353, 2346, 1801, 1623, 1601, 1583, 1455, 1435, 1382, 1247, 1208, 1108, 963, 749, 703

[a] Satisfactory microanalyses obtained C ± 0.4, H ± 0.3, N ± 0.3.
[b] Yields of isolated products.
[c] After column chromatography (silica gel, *t*-BuOMe/acetone = 90 : 10).
[d] Reaction time: 2 h.
[e] Reaction time: 4 h.
[f] After column chromatography (silica gel, petroleum ether (bp 50–70 °C)/Et2O = 1 : 1).
[g] Reaction time: 2.5 h.
[h] Reaction time: 3 h.
[i] After column chromatography (silica gel, EtOAc/hexane = 1 : 1).
[j] After column chromatography (silica gel, *t*-BuOMe/acetone = 99 : 1).



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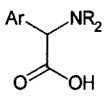

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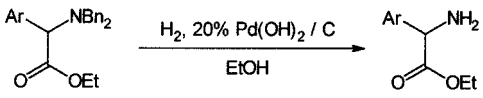

5q, r **8a, b**

Scheme 2

ature, 2 h), and then adjusting the pH of the solution to the isoelectric point with 1 N HCl.

The debenzylation of **5q,r** by heterogenous catalyzed hydrogenolysis offered the ethyl α-aryl-α-amino carboxylates **8** with a free amino functionality (Scheme 2, Table 3). *N*-debenzylation of **5q,r** was achieved with Pearlman's catalyst [20% $Pd(OH)_2$/C].[27,28]

Furthermore, there are many notable prospects. Based on our results in the formation of racemic α-aryl-α-amino acids, we also expect our method to be suitable for diastereoselective syntheses.

In summary, the aminoalkylation of phenols and aromatic *N*- and *O*-heteroaromatics with **3** provides a simple and straightforward route to a variety of ethyl α-aryl-α-amino carboxylates in good yields. Our method only utilizes inexpensive, readily available starting materials. The range of reactions using in situ generated iminium salts **3** will be extended by adding other nucleophiles, such as allylsilanes or organometallic compounds.

Table 3 Ethyl α-Aryl α-amino Carboxylates **8** with a Free Amino Group

Substrate	Product[a]	Appearance	Yield[b] (%)	^{1}H NMR (200 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	IR (film) ν (cm^{-1})
5q	**8a**	yellow oil	97[c]	1.21 (t, 3 H, *J* = 7.2, CH_2CH_3), 2.02 (br s, 2 H, NH_2), 3.74 (s, 3 H, NCH_3), 4.03–4.31 (m, 2 H, CH_2CH_3), 4.88 (s, 1 H, ArCHN), 7.03–7.36 (m, 4 H, ArH), 7.71 (d, 1 H, *J* = 7.8, ArH)	2980, 2935, 2359, 1728, 1611, 1550, 1474, 1445, 1425, 1371, 1335, 1245, 1182, 1156, 1025, 742
5r	**8b**	yellow oil	93[c,d]	1.22 (t, 3 H, *J* = 7.1, CH_2CH_3), 2.59 (br s, 2 H, NH_2), 5.67 (s, 6 H, 2 OCH_3), 4.07 – 4.27 (m, 2 H, CH_2CH_3), 4.68 (s, 1 H, ArCHN), 6.47–6.51 (m, 2 H, ArH), 7.15–7.26 (m, 1 H, ArH)	2978, 2939, 1733, 1612, 1588, 1508, 1465, 1296, 1264, 1211, 1158, 1117, 1032, 834

[a] Satisfactory microanalyses obtained C ± 0.4, H ± 0.3, N ± 0.3. For the structure of substituent Ar, see Table 2 under **5q, r**.
[b] Yields of isolated products.
[c] After column chromatography (silica gel, CH_2Cl_2/MeOH = 95 : 5).
[d] Compound **8b** is mentioned in Lit[5c] without further characterization.

Anhyd THF was freshly distilled from potassium under argon. Column chromatography on silica gel was performed with Merck Kieselgel 60 (0.040-0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 200 spectrometer, using TMS as internal standard. IR spectra were recorded on a Nicolet 510 P FT-IR spectrometer. GC/MS data were obtained from a Finnigan MAT Magnum System 240. Melting points were determined on a Mettler FP61 apparatus and are uncorrected. Elemental analyses were performed on a Perkin Elmer Elemental Analyser. Satisfactory microanalyses were obtained for the new compounds **2**, **5** and **8**: C ± 0.4, H ± 0.3, N ± 0.3.

Ethyl Glyoxylate Aminals 2; General Procedure

A solution of ethyl glyoxylate (**1**; 9.4 mL, 0.05 mol, 50% in toluene, Fluka) in toluene (30 mL) was stirred at 65°C for 1 h. First 1*H*-benzotriazol (6.0 g, 0.05 mol; Fluka) and then the secondary amine (0.05 mol) were added. The mixture was stirred for 4 h at this temperature. Afterwards, $MgSO_4$ was added to remove the water, the reaction mixture was cooled to r. t. and filtered. After removal of the solvent in vacuo, the oily crude product was crystallized from Et_2O (**2a**) or used without further purification (**2b–d**).

Ethyl α-Aryl-α-amino Carboxylates 5a–f, j–m, o, r, s; General Procedure

Method A: All reactions were conducted under argon. To generate the iminium salt, a solution of ethyl glyoxylate aminal **2** (2.5 mmol) in anhyd THF (20 mL) was cooled to 0°C. $AlCl_3$ (0.33 g, 2.5 mmol + 0.33 g, 2.5 mmol for each oxygen in the side chains of the aromatic compound **4**)[29] was added in one portion under stirring. After a reaction time of 1 h at this temperature, the aromatic compound **4** (2.5 mmol) was added and the solution heated under reflux (**5a, d–f, j–m, o, r,** and **s**: 4 h; **5b** and **c**: 5 h.) The mixture was quenched with aq sat. $NaHCO_3$ solution (50 mL) at 0°C, basified by the addition of NaOH (2 N, 20 mL) to pH 10 – 12 and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed neutral and dried ($MgSO_4$). The solvent was removed in vacuo and the residue crystallized from MeOH, purified by column chromatography on silica gel or used without further purification.

Ethyl α-Aryl-α-amino Carboxylates 5g–i, n, p, q; General Procedure

Method B: All reactions were conducted under argon. To generate the iminium salt, a solution of ethyl glyoxylate aminal **2** (2.5 mmol) in anhyd CH_2Cl_2 (30 mL) was cooled to –78°C. $TiCl_4$ (0.28 mL, 2.5 mmol) was added in one portion under stirring. After a reaction time of 0.5 h at this temperature, the aromatic compound **4** was added. The temperature was then allowed to rise to –60°C (typically 2 h). Workup follows as described in Method A. The residue was crystallized from EtOAc/hexane (1:1) or used without further purification.

Debenzylation of Ethyl α-Aryl-α-dibenzylamino Carboxylates 5q,r; General Procedure

A solution of **5q** or **5r** (0.5 mmol) in anhyd EtOH (10 mL) was stirred at r.t. in the presence of 20% $Pd(OH)_2/C$ (0.02 g) and H_2 was bubbled through the mixture until the debenzylation was completed (TLC control). After removal of the catalyst by filtration through Celite, the filtrate was evaporated to yield **8a** or **8b**.

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