A Stable, Convertible Isonitrile as a Formic Acid Carbanion [$^{-}$COOH] Equivalent and Its Application in Multicomponent Reactions

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Dedicated to Prof. Dr. Peter Welzel, Leipzig, on the occasion of his 70th birthday

Abstract: The application of 2-(2,2-dimethoxyethyl) phenyl isonitrile in Ugi, Passerini, and Ugi–Smiles reactions is described. The simple transformation to highly activated indolyl amides allows functional-group conversion of the isonitrile moiety into a variety of carboxylic acid derivatives, overall acting as a neutral, nucleophilic COOH equivalent.

Key words: multicomponent reaction, convertible isonitrile, Ugi reaction, Passerini reaction, Ugi–Smiles reaction, formyl synthon

Isonitrile-based multicomponent reactions (IMCR) are important to provide a fast and versatile access to a variety of 'small molecules' with skeletal and functional-group diversity, with minimal expenditure.[1] The Ugi four-component reaction (U-4CR) is considered to be the most important IMCR leading to peptides and peptide-like frameworks.[2,3] In addition to the U-4CR, the Passerini (P-3CR) and the Ugi–Smiles reactions are very valuable IMCR for the synthesis of highly diversified libraries.[1–7] They can be utilized for the generation of open-chained as well as macrocyclic products in one-pot procedures.[3,6,7]

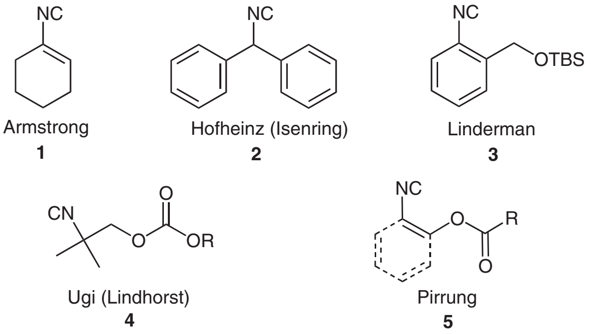
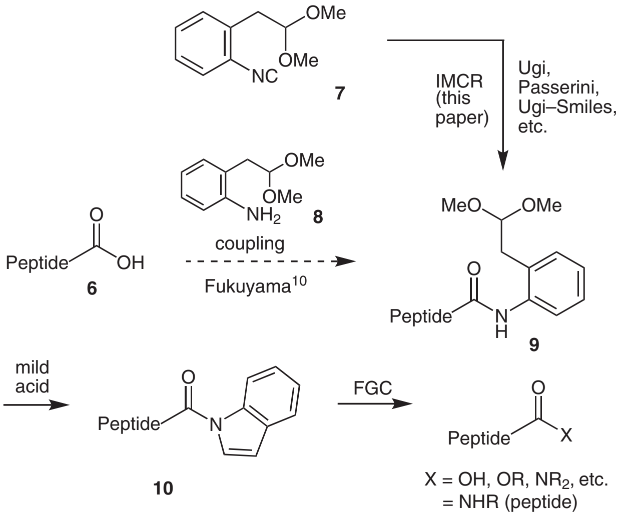


Figure 1 Convertible isonitriles

The major concern when using isonitriles as condensing agents and one-carbon building blocks is the difficult post-modification of the C-terminal amide bonds generated in these reactions. Therefore, the application of so-called convertible isonitriles for the selective conversion of this particular amide bond is highly desirable. So far, only a very limited number of convertible isonitriles has been applied, mostly for selected processes or on a small scale only (**1**–**5**, Figure 1).[8] None has led to a notable breakthrough so far. The reasons include multistage, cost-intensive access, a lack of (storage) stability, or the absence of multiple post-modification possibilities.

A well-behaved convertible isonitrile though can be considered as a neutral, carbon nucleophilic CO_2H or COX equivalent. Our continued interest in IMCR[3,6,7] required the development of a universal convertible isonitrile which (a) is simple to synthesize, (b) exhibits high stability and storability, and (c) is prone to a variety of functional-group conversions (FGC) under moderate reaction conditions. Most importantly, the reagent should be able to act as a formyl equivalent in molecules that contain amide or even nonhindered ester bonds which must remain unaffected. The temporary peptide protecting group, 2-(2,2-dimethoxyethyl) aniline (**8**), developed by Fukuyama et al. seemed to be the most appropriate one for our concept.[9,10] It is based on the formation of an activated indolyl amide **10** upon treatment of amide **9** under slightly acidic conditions (Scheme 1).



Scheme 1 Convertible isonitrile **7** as a COOH equivalent

Here, we report our findings on the use of acetal **7** as a convertible isonitrile that fulfills all aspects mentioned above, and which can be converted during or after an IMCR into the Fukuyama protecting group. From there, it can subsequently be transformed into a carboxylic acid or

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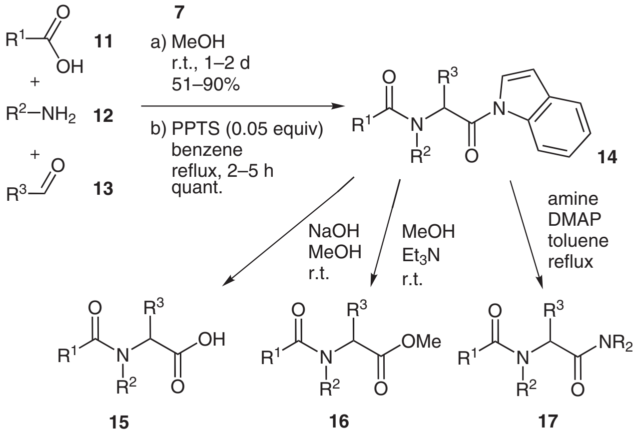
a similar derivative (Scheme 1). Isonitrile **7** is available in five steps, the overall yield is 54%.[11] The product, which can be obtained readily in multigram amounts, can be stored for weeks at 0 °C without any degradation.



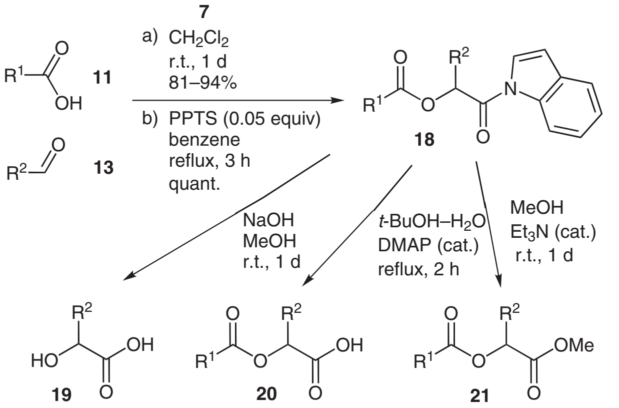
Scheme 2 Multicomponent reactions: synthesis and conversion of the Ugi-4CR-derived indolyl amide **14**[12–14]

Table 1 Conversions of Indolyl Amide **14** into Primary and Secondary Amides, Carboxylic Acids, and Methyl Esters

Entry		R^1	R^2	R^3	R	Yield (%)
1	**15a**	Me	*i*-Pr	H		78
2	**15b**	Me	Bn	H		92
3	**15c**	PMB	Bn	iPr		85
4	**16a**	Me	*i*-Pr	H		87
5	**16b**	Me	Bn	H		92
6	**17a**	Me	*i*-Pr	H	H, allyl amine	86
7	**17b**	Me	Bn	H	H, allyl amine	>99
8	**17c**	Me	*i*-Pr	H	pyrrolidine	73
9	**17d**	Me	Bn	H	pyrrolidine	89

Isonitrile **7** proved to be well-behaved in U-4CR. The α-aminoacyl amide derivatives are formed in yields ranging from 51–90%. Subsequent transformations to the indolyl amides **14** with catalytic amounts of PPTS in refluxing benzene or toluene was performed in quantitative yields. The saponification of **14** under weak basic conditions at room temperature afforded the carboxylic acid derivatives **15a–c** (Scheme 2, Table 1, entries 1–3). As expected, under these mild conditions the cleavage of the indolyl amide bonds was observed, whereas completely hydrolyzed amino acid derivatives were not detected. After methanolysis of **14** in the presence of catalytic amounts of Et$_3$N, the methyl esters **16a**,**b** were obtained in high yields. The transamidation of **14** with allyl amine provided the allyl amide derivatives **17a**,**b** (Table 1, entries 6, 7). This procedure circumvents the use of allyl isonitrile, which is very volatile and of obnoxious odor. Tertiary amides **17c**,**d** can be obtained by treatment of **14** with secondary amines like pyrrolidine (Table 1, entries 8, 9).

Isonitrile **7** is also suitable for other IMCR. Thus Passerini reactions give indolyl amides **18** in a sequence comprising the three-component condensation and the indolyl forming step in excellent yields (Scheme 3). Treatment of **18** in the presence of NaOH led to a complete saponification to α-hydroxy acids **19a**,**b** (Table 2), i.e. formally the product of an addition of a COOH$^-$ anion to an aldehyde. However, with a slightly different solvent mixture the selective hydrolysis of the amide bond in the presence of an ester bond can be accomplished. A mixture of *t*-BuOH–H$_2$O in the presence of a catalytic amount of DMAP afforded acyloxy carboxylic acid **20**. Alternatively, with MeOH in the presence of the tertiary amine Et$_3$N, the corresponding methyl ester **21** can be obtained. This intriguing transformation demonstrates the high chemoselectivity of this activated amide moiety even in the presence of a cleavable ester bond.



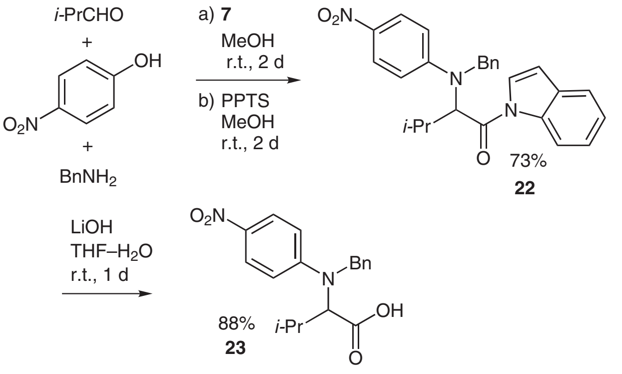
Scheme 3 Synthesis and conversion of the Passerini 3CR derived indolyl amide **18** (**a**: R^1 = PMB, R^2 = *i*-Pr; **b**: R^1 = Me, R^2 = Bn)[15,16]

Table 2 Conversions of Indolyl Amide **18** into Carboxylic Acids, Esters, and α-Hydroxy Acids (PMB = 4-Methoxybenzyl)

Entry		R^1	R^2	Yield (%)
1	**19a**	PMB	*i*-Pr	Quant.
2	**19b**	Me	Bn	Quant.
3	**20a**	PMB	*i*-Pr	63
4	**21a**	PMB	*i*-Pr	74

In Ugi–Smiles reactions, activated phenols (e.g., *o*- or *p*-nitro phenols) are used as the carboxylic acid surrogate in IMCR. The Ugi–Smiles reaction of isobutyraldehyde, benzyl amine, *p*-nitro phenol and convertible isonitrile **7** afforded indolyl amide **22** in 73% yield (Scheme 4). The conversion of **22** in the presence of LiOH led to the α-amino acid derivative **23** in 88% yield.

In summary, 2-(2,2-dimethoxyethyl)phenyl isocyanide **7** was successfully implemented of as a new convertible



Scheme 4 Multicomponent reactions: synthesis and conversion of the Ugi–Smiles derived indolyl amide **22**[17,18]

isonitrile in IMCR and as neutral formyl ‘anion’ equivalent.[19] The synthesis of **7** is simple and affordable. Further advantages are the high stability as shown in the applications in Ugi, Passerini, and Ugi–Smiles reactions. The transformations of the intermediates to carboxylic acids, methyl esters, primary and secondary amides were performed under mild conditions in good to excellent yields. The high chemoselectivity could be proven by cleavage of the indolyl amide in the presence of a cleavable ester.

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(12) **Representative Procedure for Ugi Reactions of Convertible Isonitrile 7**
Primary amine **12** (10.5 mmol) and oxo compound **13** (10.5 mmol) were dissolved in MeOH (20 mL) in the presence of Na_2SO_4 (5.30 g) and stirred for 2 h at r.t. to preform the imine. Subsequently, carboxylic acid **11** (10.46 mmol) and convertible isonitrile **7** (2.00 g, 10.46 mmol) were added and the mixture was stirred overnight. When TLC monitoring (CH_2Cl_2–MeOH, 19:1) indicated complete formation of the Ugi reaction products, the mixture was evaporated to dryness under reduced pressure. The residue was either used directly for the next step, or dissolved in EtOAc (50 mL) and H_2O (30 mL). In the latter case, the water layer was discarded and the organic layer was washed with citric acid solution (3 × 30 mL, pH 2), H_2O (2 × 30 mL), sat. $NaHCO_3$ solution (3 × 30 mL), and finally with brine (3 × 30 mL). The organic solvent was dried over Na_2SO_4, filtered, and evaporated to give the crude Ugi reaction products.

(13) **Representative Procedure for Conversions of Ugi Products into Indolyl Amides 14**
To the crude Ugi reaction products (2.92 mmol) in benzene (40 mL), pyridinium *p*-toluenesulfonate (PPTS; 37 mg, 0.15 mmol) was added as catalyst. This mixture was heated to reflux for 1.5–3 h until TLC (CH_2Cl_2–MeOH, 19:1) indicated complete conversion. The solution was cooled to r.t. and washed with H_2O (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to the give the crude indolyl amides **14a**–**d**. These were either isolated and purified, or directly converted into the corresponding carboxylic acids or derivatives.

(14) ***N*-Benzyl-*N*-[2-(1*H*-indolyl)-2-oxoethyl]acetamide (14b)**
Recrystallization of crude compound **14b** from EtOAc gave a white powder (95% recovery). TLC: $R_f = 0.86$ (CH_2Cl_2–MeOH, 19:1); mp 129–130 °C(benzene). ^1H NMR [400 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: δ = 2.15, 2.30 (2 s, 3 H, CH_3), 4.67 (s, 2 H, CH_2), 4.73 (s, 2 H, CH_2), 6.60, 6.64 (2d, *J* = 3.7 Hz, 1 H, CH), 7.19–7.39 (m, 8 H, 8 CH), 7.52 (d, *J* = 8.2 Hz, 1 H, CH), 8.39 (d, *J* = 8.1 Hz, 1 H, CH) ppm. ^{13}C NMR [100 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: δ = 21.36, 47.82, 52.74, 109.89, 116.35, 120.77, 123.48, 123.84, 125.16, 126.58, 127.85, 128.27, 128.62, 128.94, 129.93, 135.45, 135.69, 166.27, 171.44 ppm. ESI-MS of $C_{19}H_{18}N_2O_2$: *m/z* = 329.1 [M + Na$^+$], 307.2 [M + H$^+$], 305.0 [M – H$^-$]. IR (ATR): ν = 1711.5, 1634.6, 1534.7, 1485.4, 1471.0, 1450.5, 1431.1, 1383.4, 1367.5, 1350.5, 1315.5, 1262.2, 1227.7, 1202.7, 1154.7, 1108.4, 1087.7, 1040.6, 997.8, 976.6, 949.7, 918.0, 820.9, 793.9, 772.7, 746.6, 723.2, 696.1, 663.6 cm^{-1}. HRMS: *m/z* calcd for $C_{19}H_{18}N_2O_2$ [M + Na]$^+$: 329.12659; found: 329.12602.
***N*-Acetyl-*N*-benzylglycine (15b)**
Treatment of indolyl amide **14b** with methanolic NaOH (1 N, contains 5% H_2O) overnight gave carboxylic acid derivative **15b** as a light brown solid. TLC: $R_f = 0.19$ (EtOAc–MeOH, 2:1); mp 119–120 °C (EtOAc). ^1H NMR [300 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: δ = 2.16, 2.24 (2 s, 3 H, CH_3), 3.92, 4.08 (2 s, 2 H, CH_2), 4.62, 4.64 (2 s, 2 H, CH_2), 7.17–7.39 (m, 5 H, 5 CH), 10.85 (br s, 1 H, OH) ppm. ^{13}C NMR [75 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: δ = 21.02, 21.18, 46.92, 48.86, 49.61, 52.94, 126.54, 127.53, 127.85, 128.23, 128.50, 128.88, 135.18 135.98, 171.26, 172.14, 172.50,

172.69 ppm. ESI-MS of $C_{11}H_{13}NO_3$: m/z = 230.2 $[M + Na^+]$, 208.1 $[M + H^+]$, 206.1 $[M – H^–]$. IR (ATR): ν = 1712.8, 1585.6, 1484.9, 1440.6, 1398.9, 1354.2, 1247.9, 1202.3, 1173.0, 998.7, 947.1, 801.6, 751.3, 737.6, 704.3, 682.9 $cm^{–1}$. HRMS: m/z calcd for $C_{11}H_{13}NO_3$ $[M + Na]^+$: 230.07931; found: 230.07832.

Methyl *N*-Acetyl-*N*-benzylglycinate (16b)

^1H NMR [300 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: δ = 2.13, 2.22 (2 s, 3 H, CH_3), 3.71 (s, 3 H, CH_3), 3.93, 4.06 (2 s, 2 H, CH_2), 4.62, 4.64 (2 s, 2 H, CH_2), 7.18–7.39 (m, 5 H, 5 CH) ppm.

N^2-Acetyl-*N*-allyl-N^2-benzylglycine Amide (17b)

^1H NMR [400 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: δ = 2.14, 2.21 (2 s, 3 H, CH_3), 3.78–3.86 (m, 2 H, CH_2), 3.91, 3.98 (2 s, 2 H, CH_2), 4.62, 4.67 (2 s, 2 H, CH_2), 5.06–5.19 (m, 2 H, CH_2), 5.65–5.86 (m, 1 H, CH), 6.33, 6.60 (2 br s, 1 H, NH), 7.16–7.39 (m, 5 H, 5 CH) ppm.

(15) **Representative Procedure for a Passerini Reaction of Convertible Isonitrile 7**

Convertible isonitrile **7** (2.00 g, 10.46 mmol) and oxo compound **13** (10.46 mmol) were dissolved in CH_2Cl_2 (15 mL). Subsequently, carboxylic acid **11** (10.46 mmol) was added. The mixture was stirred overnight at r.t., or followed by TLC (EtOAc–MeOH, 9:1) until completion. The organic layer was washed with a sat. $NaHCO_3$ solution (4 × 10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude Passerini products.

Conversion into the indolyl amides **18a** and **18b** was achieved by procedures identical to those used for **14a**–**d**.

1-(1*H*-Indolylcarbonyl)-2-methylpropyl (4-Methoxyphenyl)acetate (18a)

After purification by column chromatography (EtOAc–PE, 1:1), the indolyl amide **18a** was obtained as a brown oil in a yield of 93%. TLC: R_f = 0.78 (EtOAc–PE, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99, 1.01 (2 d, *J* = 6.6 Hz, 6 H, 2 CH_3), 2.32–2.38 (m, 1 H, CH), 3.71 (s, 2 H, CH_2), 3.77 (s, 3 H, CH_3), 5.44 (d, *J* = 5.9 Hz, 2 H, CH_2), 6.61 (d, *J* = 3.8 Hz, 1 H, CH), 6.82–6.86 (m, 2 H, 2 CH), 7.18–7.37 (m, 4 H, 4 CH), 7.46 (d, *J* = 3.8 Hz, 1 H, CH), 7.52–7.55 (m, 1 H, CH), 8.45 (d, *J* = 8.2 Hz, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.53, 19.00, 30.76, 39.94, 55.22, 77.00, 109.81, 113.86, 116.63, 120.71, 123.94, 123.99, 125.16, 125.26, 130.07, 130.27, 135.56, 158.55, 167.81, 171.45 ppm. ESI-MS of $C_{22}H_{23}NO_4$: m/z = 388.5 $[M + Na^+]$, 366.2 $[M + H^+]$, 365.3 $[M – H^–]$. IR (ATR): ν = 1707.9, 1611.9, 1585.6, 1539.8, 1511.8, 1451.3, 1404.5, 1332.8, 1310.0, 1245.0, 1226.4, 1205.7, 1177.7, 1143.3, 1100.7, 1080.7, 1025.9, 908.0, 879.6, 855.9, 818.4, 765.6, 749.7, 726.2 $cm^{–1}$. HRMS: m/z calcd for $C_{22}H_{23}NO_4$ $[M + Na]^+$: 388.15248; found: 388.15290.

(16) **2-Hydroxy-3-phenylpropanoic Acid (19)**

α-Hydroxy acid **19** was obtained as a light brown oil. TLC: R_f = 0.54 (EtOAc–MeOH, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.90–3.19 (m, 2 H, CH_2), 4.40–4.44 (m, 1 H, CH), 7.20–7.36 (m, 5 H, 5 CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.23, 70.94, 126.61, 128.18, 129.34, 136.47, 176.11 ppm. ESI-MS of $C_9H_{10}O_3$: m/z = 189.2 $[M + Na^+]$, 167.1 $[M + H^+]$, 164.9 $[M – H^–]$. IR (ATR): ν = 3442.3, 1722.9, 1495.1, 1455.0, 1429.5, 1237.5, 1188.6, 1088.2, 1065.5, 1029.3, 1000.7, 910.2, 878.5, 793.6, 738.4, 698.2 $cm^{–1}$. HRMS: m/z calcd for $C_9H_{10}O_3$ $[M – H]^–$: 165.05517; found: 165.05592.

2-{[(4-Methoxyphenyl)acetyl]oxy}-3-methylbutanoic Acid (20)

Indolyl amide **18a** (0.25 g, 0.69 mmol) was dissolved in a mixture of *t*-BuOH (20 mL) and H_2O (10 mL). Then, DMAP (21 mg, 0.17 mmol) was added and the reaction mixture was heated at reflux for 2 h, after which TLC (EtOAc–PE, 1:1) indicated the saponification of the indolyl amide to the carboxylic acid. The reaction mixture was concentrated to a volume of 10 mL in a rotary evaporator. Saturated $NaHCO_3$ solution (15 mL) and CH_2Cl_2 (30 mL) were added. After separation of the organic layer, the water layer was extracted with CH_2Cl_2 (2 × 30 mL). Then the water layer was acidified with $NaHSO_4$ (2 M) and extracted with EtOAc (3 × 20 mL). The combined organic solutions of the acidic extraction were dried over Na_2SO_4, filtered, and evaporated to give carboxylic acid derivative **20** (0.12 g, 63%) as a slightly reddish oil. TLC: R_f = 0.69 (EtOAc–MeOH, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87–0.90 (m, 6 H, 2 CH_3), 2.12–2.21 (m, 1 H, CH), 3.59 (s, 2 H, CH_2), 3.70 (s, 3 H, CH_3), 4.80 (d, *J* = 4.2 Hz, 1 H, CH), 6.75–6.80 (m, 2 H, 2 CH), 7.10–7.17 (m, 2 H, 2 CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.04, 18.76, 30.01, 39.96, 55.21, 76.39, 113.82, 113.94, 125.41, 130.24, 158.47, 171.50, 175.05 ppm. ESI-MS of $C_{14}H_{18}O_5$: m/z = 289.1 $[M + Na^+]$, 264.9 $[M – H^–]$. IR (ATR): ν = 1720.1, 1620.3, 1611.2, 1587.8, 1512.9, 1495.7, 1461.0, 1435.1, 1378.6, 1289.9, 1246.1, 1179.3, 1036.3, 963.9, 818.6, 757.1, 729.4, 694.5 $cm^{–1}$. HRMS: m/z calcd for $C_{14}H_{18}O_5$ $[M + Na]^+$: 289.10519; found: 289.10467.

Methyl 2-{[(4-Methoxyphenyl)acetyl]oxy}-3-methylbutanoate (21)

^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.8 Hz, 6 H, 2 CH_3), 2.18–2.24 (m, 1 H, CH), 3.66 (s, 2 H, CH_2), 3.71 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3), 4.83 (d, *J* = 4.6 Hz, 1 H, CH), 6.84–6.88 (m, 2 H, 2 CH), 7.20–7.26 (m, 2 H, 2 CH) ppm.

(17) **Representative Procedure for an Ugi–Smiles Reaction of Convertible Isonitrile 7**

Benzyl amine (1.12 g, 10.46 mmol) and isobutyraldehyde (0.76 g, 10.46 mmol) were dissolved in MeOH (20 mL) in the presence of Na_2SO_4 (5.30 g) and stirred for 2 h at r.t. to preform the imine. Then *p*-nitrophenol (1,46 g, 10.46 mmol) and convertible isonitrile **7** (2.00 g, 10.46 mmol) were added and the mixture was stirred overnight. After TLC indicated the reaction to be complete (CH_2Cl_2–MeOH, 19:1), the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in EtOAc (50 mL) and H_2O (30 mL). The water layer was discarded and the organic layer was washed with citric acid solution (3 × 30 mL, pH 2), H_2O (2 × 30 mL), sat. $NaHCO_3$ solution (3 × 30 mL), and finally with brine (3 × 30 mL). It was dried over Na_2SO_4, filtered, and evaporated to give the crude Ugi–Smiles reaction product. Conversion into the activated indol was achieved by procedures identical to those used for **14a**–**d**.

***N*-Benzyl-*N*-[1-(1*H*-indol-1-ylcarbonyl)-2-methylpropyl]-4-nitroaniline (22)**

TLC: R_f = 0.91 (EtOAc–PE, 1:2); mp 113–114 °C (EtOAc). ^1H NMR [300 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: δ = 1.05, 1.13 (2 d, *J* = 6.8 Hz, 6 H, 2 CH_3), 2.81–2.94 (m, 1 H, CH), 4.62–4.88 (m, 2 H, CH_2), 5.01 (d, *J* = 10.4 Hz, 1 H, CH), 6.61 (d, *J* = 3.8 Hz, 1 H, CH), 6.77–6.93 (m, 7 H, 7 CH), 7.04–7.57 (m, 4 H, 4 CH), 8.04–8.15 (m, 3 H, 3 CH) ppm. ^{13}C NMR [75 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: δ = 19.14, 20.10, 28.43, 49.61, 65.40, 110.54, 112.02, 115.57, 116.50, 120.65, 123.27, 124.05, 125.28, 126.02, 126.20, 126.67, 128.20, 130.18, 135.49, 135.59, 138.47, 153.25, 167.27 ppm. ESI-MS of $C_{26}H_{25}N_3O_3$: m/z = 450.3 $[M + Na^+]$, 428.4 $[M + H^+]$, 426.3 $[M – H^–]$. IR (ATR): ν = 1691.8, 1590.7, 1494.5, 1449.6, 1384.2, 1315.2, 1287.3, 1251.5, 1205.5, 1160.8, 1111.5 1017.9, 973.2, 949.7, 907.1, 850.9, 822.6, 792.3, 749.5, 723.7, 691.1, 667.0 $cm^{–1}$. HRMS: not detectable.

(18) ***N*-Benzyl-*N*-(4-nitrophenyl)valine (23)**

Indolyl amide **22** (0.57 g, 1.34 mmol) is dissolved in THF

(10 mL) and H_2O (5 mL). After cooling to ca. 0 °C with an ice bath, $LiOH·H_2O$ (0.14 g, 3.35 mmol) is added. The mixture is stirred for one day, then acidified with $NaHSO_4$ (2 M) and extracted with EtOAc (5 × 30 mL). The combined organic solutions are dried over Na_2SO_4, filtered, and evaporated to give the pure carboxylic acid derivative **23** (0.39 g, 88%) as reddish oil. ^{1}H NMR [300 MHz, $CDCl_3$, *s-cis*(minor) and *s-trans*(major) isomers]: $\delta = 0.89–1.23$ (m, 6 H, 2 CH_3), 2.39–2.71 (m, 1 H, CH), 3.68, 3.71 (s, 1 H, CH), 4.24–4.87 (m, 2 H, CH_2), 6.78–6.92 (m, 2 H, 2 CH), 7.11–7.38 (m, 5 H, 5 CH), 8.01–8.17 (m, 2 H, 2 CH) ppm.

(19) During the preparation of this manuscript we became aware of advanced-online-published articles (now published in print) with a similar use of isonitrile **7** in a singular utilization in an Ugi reaction: (a) Gilley, C.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631. (b) Isaacson, J.; Gilley, C.; Kobayashi, Y. *J. Org. Chem* **2007**, *72*, 3913. (c) Vamos, M.; Ozboya, K.; Kobayashi, Y. *Synlett* **2007**, 1595.