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A Resource-Efficient and Highly Flexible Procedure for a Three-Component Synthesis of 2-Imidazolines

Niels Elders, Rob F. Schmitz, Frans J. J. de Kanter, Eelco Ruijter, Marinus B. Groen, and Romano V. A. Orru*

Department of Organic and Inorganic Chemistry, Faculty of Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

orru@few.vu.nl

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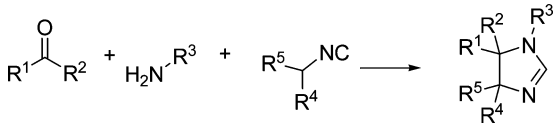

A multicomponent reaction between α-acidic isonitriles, primary amines, and carbonyl compounds was studied using 14 different solvents. Depending on the isocyanide that was used, optimal yields for the three-component synthesis of 2*H*-2-imidazolines were observed in different solvents. The solvents could be used as purchased, and in situ preformation of the imine was not required. By selecting the appropriate solvent, it was possible to considerably expand the range of compatible isocyanides toward less α-acidic isocyanides. Further process simplification was achieved by performing the reaction at higher concentrations and avoiding purification by column chromatography, resulting in a fast, easy to perform, and resource-efficient protocol for this three-component reaction.

Introduction

2-Imidazolines are an interesting class of heterocyclic scaffolds. They can be found in marine natural products with potential antiviral and antitumor activities such as topsentin and cylindrospermopsin derivatives.[1,2] More important is the widespread use of 2-imidazoline cores as synthetic intermediates for the construction of ligands relevant for applications in catalysis and medicinal chemistry.[3] In coordination chemistry and organometallic catalysis, 2-imidazolines are increasingly used as precursors for *N*-heterocyclic carbene (NHC) ligands.[4] Furthermore, they have been employed as chiral ligands in asymmetric catalysis.[5] 2-Imidazolines show great structural similarities to the widely used oxazolines[6] and have attracted considerable interest as auxiliaries in asymmetric synthesis.[7] In general, 2-imidazolines are stronger bases than the corresponding oxazolines, and tuning of the basicity, nucleophilicity, and donor

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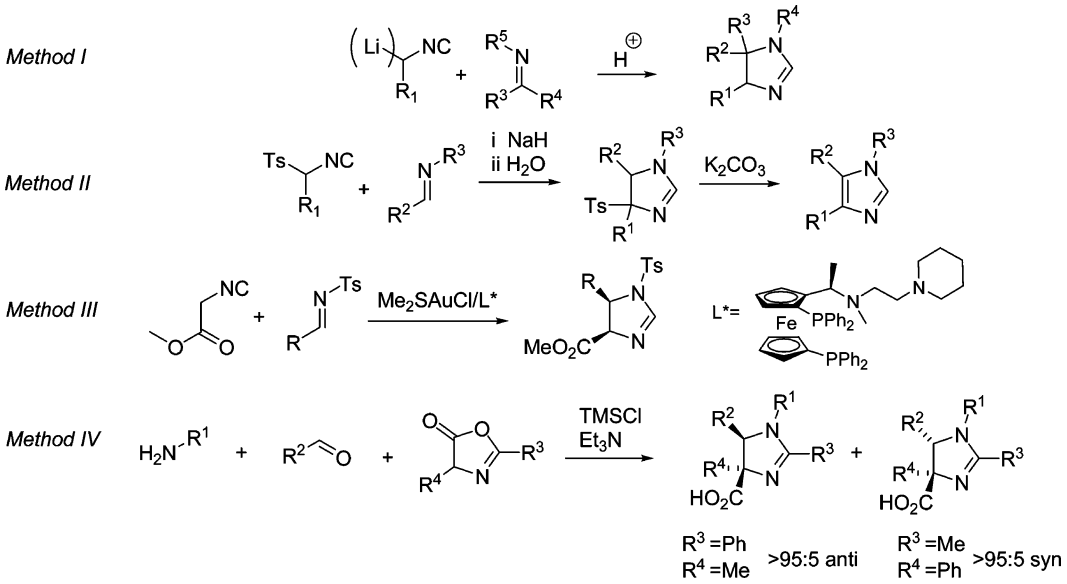
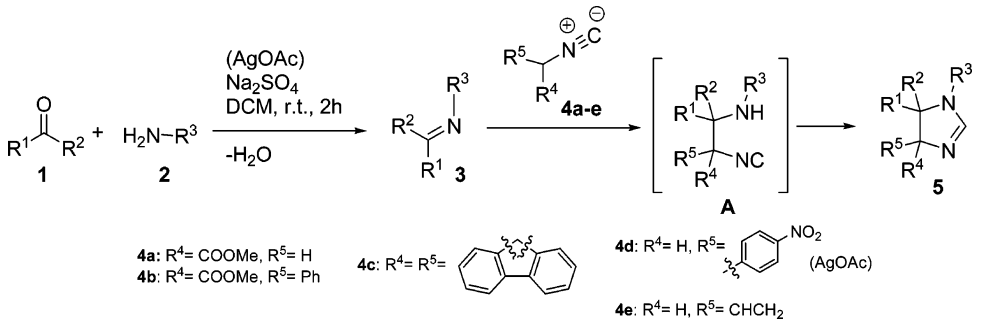
SCHEME 1. Discussed Synthetic Approaches toward 2-Imidazolines



SCHEME 2. Multicomponent Synthesis of 2*H*-2-Imidazolines



strength by changing the N1 substituent can be achieved over a much wider range.[8]

2-Imidazolines are also of considerable importance because of their wide variety of biological activities. For example, several 2-imidazolines have a high affinity for imidazoline binding sites (IBS),[9] which are involved in regulation of blood pressure, insulin secretion control, hypertension, and numerous human brain disorders such as depression, neurodegeneration, and opioid tolerance/dependence.[10] In addition, 2-imidazolines have been studied for modulation of the estrogen receptor[11] and the α2-adrenoceptor.[12] Furthermore, 2-imidazolines have been studied as, among others, antihyperglycemic,[13] anti-inflammatory,[14] antihypertensive,[12,15] antihypercholesterolemic,[16] and antidepressant[17] agents. 2-Imidazolines are also used as convenient building blocks for the synthesis of azapenams, (bis)-dioxocyclams, and diazepinones.[18] Suitably functionalized 2-imidazolines are easily converted to 2,3-diamino acids, which are incorporated in a wide range of antibiotics and other biologically active compounds.[19] Moreover, a series of highly substituted *cis*-imidazoline analogues called nutlins (Nutley inhibitors) have been successfully screened as inhibitors of MDM2, a protein that negatively modulates the transcriptional activity and stability of the p53 tumor suppressor protein.[20] Consequently, 2-imidazolines are an attractive synthetic target for several areas of chemical and pharmaceutical research.

A traditional synthetic approach toward 2-imidazolines is the ring closure of 1,2-diamines,[21] which is rather limited in scope. In addition to this, a range of methods are available for the synthesis of 2-imidazolines.[22−25] For example, a well-known approach involves the reaction of isocyanoacetates or α-lithiated

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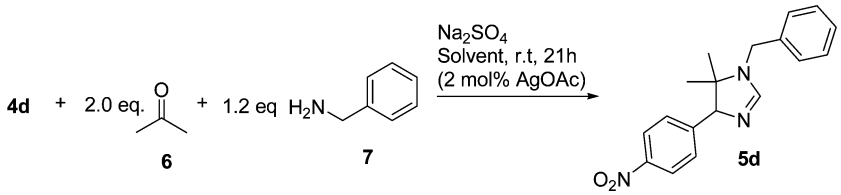
SCHEME 3



isocyanides with imines (Scheme 1, Method I).[22a] In a related procedure, tosylmethyl isocyanide (TosMIC) can be employed (Method II). Some catalytic diastereo- and enantioselective routes toward 2-imidazolines using chiral ferrocene-based catalysts have also been reported, although this only proved successful when *N*-tosylimines were employed (Method III).[22b−f]

A powerful alternative strategy for the rapid introduction of molecular diversity involves multicomponent reactions (MCRs).[26] A recently reported multicomponent synthesis of 2-imidazolines involves the TMSCl-mediated 1,3-dipolar cycloaddition of oxazolones to in situ generated imines, which affords C2-substituted 2-imidazolines diastereoselectively (Scheme 1, Method IV).[25] The diastereochemical outcome of the reaction is dictated by the oxazolone substituents. Recently, we have also contributed in this area and reported a flexible MCR for the synthesis of 2*H*-2-imidazolines suitable for combinatorial applications.[27] In situ preformation of the imine by stirring an aldehyde and a primary amine in DCM followed by the addition of an α-acidic isonitrile afforded the corresponding 2-imidazolines in moderate to good yields (Scheme 2). The mechanism for this MCR probably involves a Mannich-type addition of deprotonated isocyanide **4** to (protonated) imine **3** followed by ring closure of intermediate **A**. However, a concerted cycloaddition of **3** and deprotonated **4** to produce **5** cannot be excluded.[28]

Although the application of the simplest isocyanoacetate (**4a**, $R^4 = CO_2Me$, $R^5 = H$) did not give satisfying results, somewhat more reactive isocyanides (**4b** and **4c**) provide the corresponding 2-imidazolines smoothly using DCM as the solvent. In both the amine and the aldehyde components, a wide variety of aliphatic, aromatic, heteroaromatic, and olefinic substituents are allowed. When **4b** was applied, the diastereoselectivity of the reaction was only moderate but always in favor of the isomers with the large substituents cis to each other. The scope of the MCR was considerably extended by the application of ketones as the carbonyl input. However, in these cases the use of catalytic amounts of AgOAc was found to be essential.[28] Also, the use of *p*-nitrobenzyl isocyanide (**4d**) in our MCR was only successful in the presence of AgOAc. However, the use of allyl isocyanide (**4e**) remained without success. Density functional theory calculations showed that the proton affinity, the energy of the HOMO of the α-anion, as well as the contribution of the carbanion (p_z) orbital in the HOMO are important features that can rationalize the reactivity of the various isocyanides. This led us to believe that the type of solvent used plays a crucial role in the performance of this three-component condensation reaction. Thus far, DCM was the solvent of choice to obtain optimal yields of 2-imidazolines. However, with **4b** as the isocyanide input, MeOH, toluene, and DCM are all solvents in which the MCR runs efficiently.[27] Furthermore, preliminary studies for isocyanide **4a**, which otherwise reacts sluggishly, indicate that the MCR can yield a 2-imidazoline using MeOH as the solvent, albeit in moderate yield. These considerations prompted us to study the influence of the solvent on the performance of the three-component reaction (3-CR) for 2-imidazolines. In particular, the relation between the solvent used and the scope of compatible isocyanide inputs was investigated in more detail. The results of this study are presented here.

Results and Discussion

From our earlier studies, it was known that *p*-nitrobenzylisocyanide (**4d**) and acetone (**6**) are relatively poor inputs for the 3-CR. Using DCM as the solvent, we found that the corresponding 2-imidazolines were only formed in the presence of AgOAc.[28] Consequently, we decided to use the reaction between *p*-nitrobenzylisocyanide (**4d**), acetone (**6**), and benzylamine (**7**) for the synthesis of imidazoline **5d** to study the influence of the type of solvent on the performance of the 3-CR (Scheme 3). We studied the reaction in 14 different solvents ranging from polar aprotic and polar protic to very apolar. All experiments were performed at a concentration of 0.1 M of **4d**

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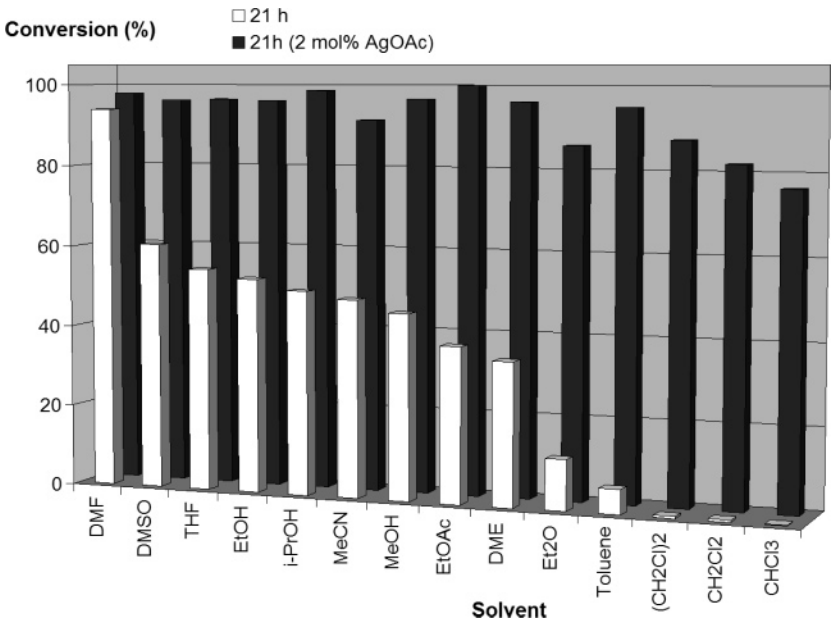

FIGURE 1. Conversion of the MCR for imidazoline **5d** using **4d**, **6**, and **7** in different solvents.

TABLE 1. Data Solvent Study without AgOAc[a]

					conversion (%) after			
entry	solvent	μ/D[b]	ϵ[c]	E_T^N[d]	0.25 h	2 h	5 h	21 h
1	DMF	3.82	38.25	0.386	1	17	42	94
2	DMSO	3.96	47.24	0.444	2	24	43	61
3	THF	1.75	7.52[e]	0.207	1	5	17	55
4	EtOH	1.69	25.3	0.654	0	5	16	53
5	MeCN	3.92	36.64	0.460	0	5	15	48
6	MeOH	1.70	33.0	0.762	2	5	15	46
7	*i*-PrOH	1.56	20.18	0.546	0	3	11	50
8	EtOAc	1.78	6.08	0.228	0	3	10	38
9	DME		7.30[f]	0.231	0	2	8	35
10	Et_2O	1.15	4.27	0.117	0	1	2	12
11	toluene	0.37	2.38[g]	0.099	0	0	0	6
12	$(CH_2Cl)_2$	1.80	10.42	0.327	0	0	0	0
13	CH_2Cl_2	1.60	8.93[g]	0.309	0	0	0	0
14	$CHCl_3$	1.04	10.0[e]	0.259	0	0	0	0

[a] All reactions were performed in duplicate at 0.5 mmol scale (0.1 M). Reported conversions are the mean values of duplicate experiments. Reproducibility was usually within 3% variation. Conversions were determined by HPLC: Pathfinder AS column, NH_4OAc buffer (pH 7.32)/acetonitrile (63:37), 30 °C, 1.0 mL/min. **4d** (2.0 min, 274 nm), **5d** (4.8 min, 267 nm), and 2,2′-dinitrobiphenyl (I.S., 10.9 min, 264 nm). [b] μ: electric dipole moment in debye units.[29] [c] ϵ: dielectric constant (relative permittivity);[29] at 293 K unless stated otherwise. [d] E_T^N: dimensionless normalized solvent polarity scale, using H_2O (1.000) and TMS (0.000) as extreme polar and nonpolar reference solvents (measured at 25 °C and 1 bar).[30] [e] At 295 K. [f] At 296 K. [g] At 298 K.

to ensure that the isocyanide was completely dissolved. Furthermore, all reactions were run in duplicate in the presence and in the absence of AgOAc. The formation of **5d** was followed in time by HPLC using 2,2′-dinitrobiphenyl as internal standard. In all cases, acetone (**6**) was added as the final component to examine the performance of the MCR without preformation of the imine. The data are summarized in Figure 1 and Table 1.

In the majority of the solvents used, 2-imidazoline **5d** could be detected after 21 h at room temperature, which demonstrates that the MCR can be performed without in situ preformation of the imine. Also, all solvents were used as purchased and did not require drying before use, which shows that the experimental procedure indeed is very robust. In the presence of AgOAc, the 3-CR proceeds smoothly. In all solvents, a conversion between 80 and 100% was observed (Figure 1, black bars). However, under these conditions, no general trends for the conversion of the isocyanide **4d** in relation to the nature of the investigated solvents could be observed. In the absence of the AgOAc catalyst, however, the reaction was found to be strongly solvent dependent (Figure 1, white bars). As reported previously,[28] 2-imidazoline **5d** could not be detected in DCM. Also, in chloroform and 1,2-dichloroethane **5d** was not formed, suggesting that chlorinated solvents should be avoided for this combination of inputs. In all other solvents studied, product formation was observed even without the use of AgOAc (Figure 1 and Table 1).

The data generally indicate a correlation between solvent polarity and conversion. The conversions are definitely higher in polar (aprotic) solvents such as DMSO and DMF compared to those in apolar solvents such as toluene. The initial conversion in DMSO seems somewhat higher as compared to that in DMF (Table 1, entries 1 and 2). However, in DMSO formation of **5d** stops at 61%, whereas in DMF **5d** was formed in 94% after 21 h (entry 1).[31] Although in general the 3-CR performs better in more polar solvents, no clear relation between electrostatic parameters such as the dipole moment (μ/D) or the dielectric constant (ϵ) of the solvent and the conversion can be concluded. For example, conversions were found to be higher in THF than in MeOH, EtOH, or MeCN (entries 3−6). Because the electrostatic approach neglects specific solute/solvent interactions, it often fails in correlating observed solvent effects with physical solvent parameters.[30a] Reichardt and Harbusch-Görnert introduced a multiparameter solvent polarity scale (E_T^N) to define "solvent polarity" as the overall solvation capability (or solvation power).[30b] However, also no clear correlation between the normalized dimensionless E_T^N values and the conversion

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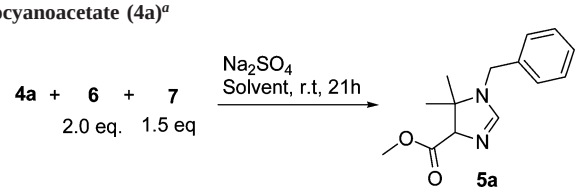
(31) Thirty-five percent of unreacted **4d** could be isolated from a separate reaction at 2 mmol scale.

TABLE 2. Solvent Study for the MCR Using Methyl Isocyanoacetate (4a)[a]



		conversion (%) after		
entry	solvent	2 h	5 h	24 h
1	MeOH	87	98	98
2	EtOH[b]	81	98	98
3	*i*-PrOH	59	83	83
4	DCM	24	48	92
5	EtOAc	33	45	82
6	THF	23	35	86
7	MeCN	30	33	52
8	DMF	62	64	74

[a] Reactions were performed at 0.5 mmol scale (0.2 M). Acetone (**6**) was added as the final substrate to prevent the preformation of imine. Conversions were determined by ^{1}H NMR. [b] Transesterification was observed (**5a**/ethyl ester = 45:55 after 5 h).

could be observed. It should be realized that three different reactions proceed in one pot for the investigated 3-CR: initial imine formation, subsequent Mannich-type addition, followed by cyclocondensation. The kinetics may differ for unrelated solvents and may therefore be hard to establish precisely. This probably also accounts for the fact that the 3-CR using **4b**, isobutyraldehyde, and isopropylamine as inputs performs similarly well in MeOH, toluene, and DCM, as was reported by us earlier.[27]

These observations led us to reinvestigate the performance of the 3-CR using methyl isocyanoacetate (**4a**) as the isocyanide input (Table 2). When this isocyanide was combined in one pot with benzaldehyde and benzylamine (**7**), the corresponding 2-imidazoline was only formed in poor yields.[27] To directly compare the 3-CR using **4a**, with the reaction affording **5d** as described above, **4a** was combined with acetone (**6**) as the carbonyl component and **7** using a similar protocol as for the 3-CR using **4b**. In contrast to our earlier findings, conversion of **4a** to the 2-imidazoline **5a** went smoothly at room temperature using a range of different solvents (Table 2). Apparently, the difference in reactivity arises from the carbonyl component used. Presumably, the electrophilicity of the (protonated) intermediate imine determines the efficiency of the subsequent Mannich-type addition of the α-acidic isocyanide.

As noted above, the conversions after 24 h for the MCR using **4a** were good to excellent. The results show that after 2 h the reaction was almost complete in MeOH and EtOH (87 and 81% conversion, respectively). However, in other solvents the 3-CR proceeds more slowly. Thus, when **4a** is used as the isocyanide input, protic polar solvents give optimal conversions. After the initial deprotonation of **4a** by, for example, the imine, the resulting anion may be more efficiently stabilized by hydrogen bonding with the solvent, resulting in a higher concentration of the reactive species.

Scope of Compatible Isocyanides. The results described above show that the MCR using methyl isocyanoacetate (**4a**) in MeOH is complete within 5 h even without the use of a catalyst. Therefore, we decided to explore the scope of compatible isocyanides in this reaction in further detail. Thus, six additional α-isocyano esters (**4f**−**k**) with different α-substituents were used as input for the MCR together with acetone (**6**) and benzylamine (**7**) in MeOH as the solvent (Table 3). Generally, the α-isocyano esters were prepared via slight modifications of standard protocols,[27,32] in three steps from their corresponding α-amino acids, without the use of chromatographic purification (Scheme 4).

SCHEME 4. α-Isocyano Esters Synthesis

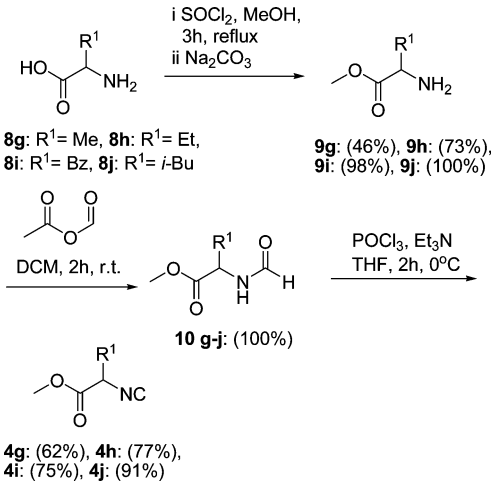
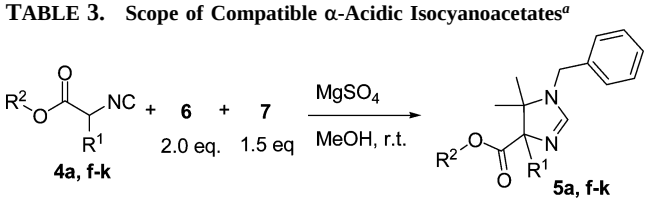


TABLE 3. Scope of Compatible α-Acidic Isocyanoacetates[a]



entry	isonitrile	R^1	R^2	time	conversion[b] (isolated yield)[c] (%)
1	**4a**	H	Me	5 h	98 (89)
2	**4f**	H	*t*-Bu	22 h	100 (98)
3	**4g**	Me	Me	22 h	96 (80)
4[d]	**4g**	Me	Me	48 h	93 (90)
5[d,e]	**4g**	Me	Me	8 h	91 (89)
6	**4h**	Et	Me	48 h	90 (73)
7	**4i**	Bn	Me	48 h	100 (quantitative)
8	**4j**	*i*-Bu	Me	48 h	82 (77)
9[f]	**4k**	*i*-Pr	Me	4 weeks	84 (57)
10[d−f]	**4k**	*i*-Pr	Me	4 weeks	66
11[d,e,g]	**4k**	*i*-Pr	Me	2 weeks	100 (quantitative)

[a] Unless stated otherwise, reactions were performed at 1.0 mmol scale (0.2 M). Acetone (**6**) was added as the final substrate to prevent preformation of imine. [b] Conversions were determined by ^{1}H NMR. [c] Isolated yield was determined from a separate reaction at 2.0 mmol scale. [d] Substrates were mixed at a 1:1:1 ratio, workup by extraction only. [e] Reaction performed at 2.0 M, 2.0 mmol scale. [f] In the presence of 2 mol % AgOAc. [g] In the presence of 10 mol % AgOAc.

All isocyanides afforded the desired 2-imidazolines **5a**,**f**−**k** in good to excellent isolated yields (Table 3). For example, application of **4f** with a sterically demanding substituent R^2 gave the corresponding 2-imidazoline **5f** in 98% isolated yield (entry 2). However, it should be noted that to reach completion the reaction took 22 h at room temperature. In addition, the use of isocyanide **4g**, with a methyl group at the α-carbon, resulted in a similarly efficient but somewhat slow reaction (entry 3). The conversion was high (96%), but the product **5g** was only isolated

(32) Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400−402.

in 80% yield. According to the ^{1}H NMR spectrum of the crude reaction mixture, this MCR proceeds without the formation of any side products. Therefore, the observed loss of material most likely occurs during the purification by column chromatography. However, column chromatography can be avoided by mixing the isocyanide **4g**, acetone (**6**), and benzylamine (**7**) in equimolar amounts. After the reaction, simple extraction and evaporation of solvents then affords the corresponding 2-imidazoline **5g** in good isolated yield (entry 4). The slower conversion (93% after 48 h) arising from the lower concentration of the intermediate imine was compensated by performing the reaction at 2.0 M concentration. At this concentration, a similar conversion (91%, entry 5) was already observed after 8 h at room temperature, thus resulting in a faster, easier, and more resource-efficient protocol for the 3-CR.

The results presented in Table 3 also show that reaction rates decrease as the steric bulk of the α-substituents R^1 increases. When isocyanides **4h**−**j** were used as starting materials in this reaction, generally 48 h are required to achieve good to excellent conversion (entries 6−8). The conversions toward the corresponding imidazolines **5h**−**j** decrease in the order of R^1 = benzyl > ethyl > *i*-butyl. This suggests that, in addition to steric effects, also electronic effects of the R^1 substituent influence the progress of our 3-CR. The reaction with isocyanide **4k** (with R^1 = isopropyl) seems to approach the limits for this MCR. After stirring **4k**, acetone (**6**), and benzylamine (**7**) for two weeks in MeOH at room temperature, we could detect only unreacted isocyanide **4k** and the corresponding imine. Heating the reaction mixture at reflux temperature for 2 weeks also did not result in the formation of detectable amounts of 2-imidazoline **5k**. However, when AgOAc was added as catalyst, 2-imidazoline **5k** was found in a very acceptable 84% conversion, although a long reaction time (4 weeks) was required to achieve this conversion. Increasing the concentrations of the inputs did not result in a significant improvement (entry 10), but using increased amounts of AgOAc (10 mol %) afforded 2-imidazoline **5k** quantitatively after 2 weeks (entry 11).

Conclusions

Depending on the isocyanide used, optimal yields for the three-component synthesis of 2*H*-2-imidazolines are observed in different solvents. Although a wide range of solvents can be used efficiently as the reaction medium, in general, MeOH proved to be a good to excellent solvent for the MCR. AgOAc is an efficient catalyst for this reaction; however, most of the reactions performed very well without this catalyst. In this MCR the solvents can be used as purchased, and in situ preformation of the imine is not necessary. With MeOH as the solvent, it was possible to considerably expand the range of compatible isocyanides toward less α-acidic isocyanides. Further process simplification was achieved by performing the reaction at higher concentrations and avoiding purification by column chromatography, resulting in a fast, easy to perform, and resource-efficient protocol for this 3-CR. The high conversions, absence of side products, and large range of compatible reaction media makes in situ follow-up chemistry for this MCR feasible.

Experimental Section

For the general experimental section, see the Supporting Information.

General Procedure 1: Reaction of 4d, 6, and 7 in Different Solvents. One milliliter of either stock solution **1** (**4d** (0.50 M) and 2,2′-dinitrobiphenyl (0.17 M) in DCM) or stock solution **2** (**4d** (0.50 M), 2,2′-dinitrobiphenyl (0.17 M) and AgOAc (0.010 M) in DCM) was transferred to a 10-mL reaction vial and evaporated to dryness under reduced pressure. Five milliliters of the appropriate solvent, 100 mg of Na_2SO_4, 65 μL of benzylamine (**7**) (0.60 mmol, 1.2 equiv), and 75 μL of acetone (**6**) (1.0 mmol, 2.0 equiv) were added, and the reaction mixture was stirred for 21 h. Aliquots (40 μL) were taken 0.25, 1, 2, 5, and 21 h after the addition of acetone, quenched in a 0.1 M (aq) HCl/MeCN mixture (30:70), and analyzed by HPLC (Shimadzu Pathfinder AS column (150 × 4.6 mm), NH_4-OAc buffer (pH 7.32)/acetonitrile (63:37), 30 °C, 1.0 mL/min. **4d** (2.0 min, 274 nm), **5d** (4.8 min, 267 nm), and 2,2′-dinitrobiphenyl (I.S., 10.9 min, 264 nm)).

General Procedure 2: Reaction of 4a, 6, and 7 in Different Solvents. A 10-mL reaction vial was charged with isocyanide **4a** (0.50 mmol), the appropriate solvent (2.5 mL), Na_2SO_4 (50 mg), benzylamine (**7**) (65 μL, 64 mg, 0.60 mmol), and acetone (**6**) (75 μL, 59 mg, 1.0 mmol). Aliquots (200 μL) were taken 2, 5, and 24 h after the addition of acetone, filtered, evaporated to dryness, and analyzed by ^{1}H NMR ($CDCl_3$).

General Procedure 3: Synthesis of Isocyanides (4g−**j).** Unless stated otherwise, $SOCl_2$ (18.0 mL, 29.4 g, 245 mmol) was added dropwise at 0 °C to a stirred solution of the corresponding amino acid **8g**−**j** (or amino acid·HCl salt) (100 mmol) in methanol (190 mL). The reaction mixture was heated for 3 h at reflux temperature followed by evaporation of all volatiles under reduced pressure to produce the methyl ester·HCl salt as a colorless solid in quantitative yield. Semisaturated Na_2CO_3 (aq) (100 mL) was added, and the mixture was extracted with DCM (4 × 100 mL). The organic layers were combined and dried over $MgSO_4$. Removal of the solvent under reduced pressure allowed isolation of the corresponding methyl ester **9g**−**j** (46−100%).

Acetic formic anhydride (prepared by stirring 1 equiv of acetic anhydride and 1.1 equiv of formic acid for 2 h at 55 °C; 15 mL, 16.8 g, 110 mmol) was added dropwise at 0 °C to a stirred solution of the appropriate methyl ester **9g**−**j** (50 mmol) in DCM (135 mL), and the mixture was stirred for 2 h at room temperature. All volatiles were evaporated under reduced pressure, and the corresponding formamide **10g**−**j** was isolated in quantitative yield.

A solution of $POCl_3$ (2.9 mL, 4.8 g, 31 mmol) in THF (60 mL, dried over KOH) was added dropwise to a solution of a formamide **10g**−**j** (25 mmol) in Et_3N (17 mL) and THF (60 mL, dried over KOH) at −78 °C. The reaction mixture was stirred for 2 h at 0 °C, and the resulting red mixture was added to cold H_2O (60 mL) and extracted with Et_2O (3 × 60 mL). The organic layers were combined, washed with H_2O (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the desired (racemic) isonitrile **4g**−**j** (65−91%), which was sufficiently pure for follow-up chemistry.

(±)-Methyl 2-Isocyanopropanoate (4g).[33] General procedure 3 was followed using DL-alanine (**8g**) (8.91 g, 100.0 mmol) to give **(±)-4g** (1.74 g, 15.4 mmol, 62%) as a red oil. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 4.34 (q, ^3J = 7.2 Hz, 1H), 3.83 (s, 3H), 1.66 (d, ^3J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$) δ (ppm) 167.5 (C), 159.6 (C), 53.3 (CH_3), 51.5 (CH), 19.3 (CH_3); IR (KBr) 2588 (s), 2145 (s), 1755 (s), 1455 (m), 1216 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 86 (100) $[M - CNH]^+$, 72 (20) $[C_3H_4O_2]^+$, 58 (25) $[C_2H_2O_2]^+$.

(±)-Methyl 2-Isocyanobutanoate (4h). General procedure 3 was followed starting from dl-α-aminobutyrate hydrochloride (**9h**·HCl) (5.0 g, 32.5 mmol). The dehydration step was performed at 23.6 mmol scale, furnishing **(±)-4h** (2.31 g, 18.2 mmol, 77%) as a red oil. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 4.24 (dd, ^3J = 5.4 Hz, ^3J = 7.4 Hz, 1H), 3.82 (s, 3H), 2.03−1.93 (m, 2H), 1.09 (t, ^3J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100.62 MHz, $CDCl_3$) δ (ppm) 167.1

(33) (a) Maeda, I.; Togo, K.; Yoshida, R. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1407−1410. (b) Uban, R.; Marquarding, D.; Seidel, P.; Ugi, I.; Weinelt, A. *Chem. Ber.* **1977**, *110*, 2012−2015.

(C), 160.1 (C), 57.7 (CH), 53.2 (CH_3), 26.3 (CH_2), 9.6 (CH_3); IR (KBr) 2980 (s), 2149 (s), 1757 (s), 1439 (m), 1212 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 100 (58) $[M - CHN]^+$, 86 (80) $[M - C_2H_3N]^+$, 72 (6) $[C_3H_4O_2]^+$, 58 (100) $[C_2H_2O_2]^+$.

(±)-Methyl 2-Isocyano-3-phenylpropanoate (4i).[33b,34] General procedure 3 was followed using L-phenylalanine (**8i**) (16.5 g, 100.0 mmol) to give **(±)-4i** (3.56 g, 18.8 mmol, 75%) as a colorless solid. Mp: 43−45 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 7.35−7.23 (m, 5H), 4.47 (dd, ^3J = 5.0 Hz, ^3J = 8.2 Hz, 1H), 3.78 (s, 3H), 3.30−3.03 (m, 2H); ^{13}C{^{1}H} NMR (100.62 MHz, $CDCl_3$) δ (ppm) 166.5 (C), 161.1 (C), 134.3 (C), 129.2 (2 CH), 128.8 (2 CH), 127.8 (CH), 58.0 (CH), 53.4 (CH_3), 38.9 (CH_2); IR (KBr) 3296 (br, s), 2950 (m), 2155 (s), 1755 (s), 1444 (m), 1221 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 162 (5) $[M - CHN]^+$, 157 (10) $[M - CH_4O]^+$, 130 (48) $[M - C_2H_3O_2]^+$, 91 (100) $[C_7H_7]^+$, 77 (16) $[C_6H_5]^+$.

(±)-Methyl 2-Isocyano-4-methylpentanoate (4j).[33b,35] General procedure 3 was followed using DL-leucine (**8j**) (13.1 g, 100.0 mmol) to give **(±)-4j** (3.53 g, 22.7 mmol, 91%) as a red oil. ^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 4.28 (dd, ^3J = 4.7 Hz, ^3J = 9.6 Hz, 1H), 3.82 (s, 3H), 1.94−1.80 (m, 2H), 1.72 (m, 1H), 0.98 (m, 6H); ^{13}C{^{1}H} NMR (100.62 MHz, $CDCl_3$) δ (ppm) 167.6 (C), 160.1 (C), 55.1 (CH), 53.2 (CH_3), 41.3 (CH_2), 24.8, 22.5, and 20.9 (2 CH_3 and CH); IR (KBr) 3337 (w), 2956 (s), 2148 (s), 1756 (s), 1469 (m), 1273 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 128 (80) $[M - CHN]^+$, 114 (10) $[M - C_2H_3N]^+$, 99 (14) $[M - C_4H_8]^+$, 86 (100) $[M - C_4H_7N]^+$.

General Procedure 4: Synthesis of 2-Imidazolines 5a,f−k. An isocyanide **4a**,**f**−**k** (2.0 mmol), benzylamine (**7**) (330 μL, 321 mg, 3.0 mmol, 1.5 equiv), acetone (**6**) (300 μL, 232 mg, 4.0 mmol, 2.0 equiv), and $MgSO_4$ (200 mg) were stirred in methanol (10 mL) until complete consumption of **4** (monitored by ^{1}H NMR). Water (15 mL) was added, and the resulting mixture was extracted with DCM (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the resulting 2-imidazoline was purified by column chromatography (Al_2O_3, EtOAc/MeOH gradient, unless stated otherwise).

Methyl 1-Benzyl-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5a).[22a] General procedure 4 was followed using **4a** (198 mg, 2.0 mmol). Five-hour reaction time followed by column chromatography (SiO_2, 5% MeOH in EtOAc containing 0.33% Et_3N, R_f 0.16) furnished **5a** (440 mg, 1.8 mmol, 89%) as a yellow oil.

^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 7.37−7.29 (m, 5H), 6.88 (d, ^4J = 1.3 Hz, 1H), 4.44 (d, ^4J = 1.3 Hz, 1H), 4.23 (d, ^2J = 15.1 Hz, 1H), 4.18 (d, ^2J = 15.1 Hz, 1H), 3.76 (s, 3H), 1.35 (s, 3H), 1.10 (s, 3H); ^{13}C{^{1}H} NMR (62.90 MHz, $CDCl_3$) δ (ppm) 171.5 (C), 156.7 (CH), 137.8 (C), 128.7 (2 CH), 127.7 (2 CH), 127.7 (CH), 79.0 (CH), 64.7 (C), 51.9 (CH_3), 46.0 (CH_2), 27.2 (CH_3), 20.1 (CH_3); IR (KBr) 3010 (m), 2854 (s), 1957 (w), 1747 (s), 1598 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 246 (12) $[M]^+$, 231 (4) $[M - CH_3]^+$, 187 (98) $[M - C_2H_3O_2]^+$, 155 (4) $[M - C_7H_7]^+$, 91 (100) $[C_7H_7]^+$; HR-MS (EI, 70 eV) calcd for $C_{14}H_{18}N_2O_2$ (M^+) 246.13683, found 246.13682.

***tert*-Butyl 1-Benzyl-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5f).** General procedure 4 was followed using **4f** (282 mg, 2.0 mmol). After 22 h reaction time, **5f** (567 mg, 1.9 mmol, 98%) could be isolated as a colorless solid.

Mp: 87−90 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 7.33−7.27 (m, 5H), 6.87 (d, ^4J = 1.2 Hz, 1H), 4.29 (d, ^4J = 1.2 Hz, 1H), 4.21 (d, ^2J = 15.2 Hz, 1H), 4.17 (d, ^2J = 15.2 Hz, 1H), 1.49 (s, 9H), 1.32 (s, 3H), 1.15 (s, 3H); ^{13}C{^{1}H} NMR (62.90 MHz, $CDCl_3$) δ (ppm) 170.0 (C), 156.4 (CH), 138.1 (C), 128.7 (2 CH), 127.6 (2 CH), 127.6 (CH), 81.2 (C), 79.3 (CH), 64.5 (C), 45.9 (CH_2), 28.1 (3 CH_3), 27.2 (CH_3), 20.0 (CH_3); IR (KBr) 2977 (m), 2840 (w), 1744 (s), 1589 (s), 1152 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 288 (2) $[M]^+$, 187 (100) $[M - C_5H_9O_2]^+$, 91 (65) $[C_7H_7]^+$; HR-MS (EI, 70 eV) calcd for $C_{17}H_{24}N_2O_2$ (M^+) 288.18378, found 288.18346.

Methyl 1-Benzyl-4,5,5-trimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5g). General procedure 4 was followed using **4g** (226 mg, 2.0 mmol). Twenty-two hour reaction time followed by column chromatography (Al_2O_3, EtOAc, R_f 0.30) furnished **5g** (417 mg, 1.6 mmol, 80%) as a yellow oil.

^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 7.37−7.29 (m, 5H), 6.81 (s, 1H), 4.19 (d, ^2J = 15.2 Hz, 1H), 4.13 (d, ^2J = 15.2 Hz, 1H), 3.75 (s, 3H), 1.36 (s, 3H), 1.25 (s, 3H), 1.05 (s, 3H); ^{13}C{^{1}H} NMR (62.90 MHz, $CDCl_3$) δ (ppm) 174.0 (C), 154.9 (CH), 138.2 (C), 128.7 (2 CH), 127.6 (CH), 127.5 (2 CH), 78.9 (C), 66.3 (C), 51.9 (CH_3), 45.8 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 20.5 (CH_3); IR (KBr) 3016 (m), 2840 (s), 1959 (w), 1731 (s), 1600 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 260 (2) $[M]^+$, 201 (100) $[M - C_2H_3O_2]^+$, 169 (6) $[M - C_7H_7]^+$, 91 (48) $[C_7H_7]^+$; HR-MS (EI, 70 eV) calcd for $C_{15}H_{20}N_2O_2$ (M^+) 260.15248, found 260.15237.

Alternatively, **4g** (226 mg, 2.0 mmol), benzylamine (**7**) (220 μL, 214 mg, 2.0 mmol), acetone (**6**) (150 μL, 116 mg, 2.0 mmol), and $MgSO_4$ (100 mg) were stirred in methanol (1 mL) for 8 h at room temperature. Water (15 mL) was added, and the resulting mixture was extracted with DCM (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to yield pure **4g** (464 mg, 1.78 mmol, 89%).

Methyl 1-Benzyl-4-ethyl-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5h). General procedure 4 was followed using **4h** (250 mg, 2.0 mmol). Forty-eight hour reaction time followed by column chromatography (Al_2O_3, EtOAc/pentane (5%), R_f 0.63) furnished **5h** (399 mg, 1.5 mmol, 73%) as a pale yellow oil.

^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 7.37−7.28 (m, 5H), 6.81 (s, 1H), 4.20 (d, ^2J = 15.2 Hz, 1H), 4.11 (d, ^2J = 15.2 Hz, 1H), 3.76 (s, 3H), 1.94−1.86 (m, 1H), 1.63−1.55 (m, 1H), 1.25 (s, 3H), 1.04 (s, 3H), 0.96 (t, ^3J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (62.90 MHz, $CDCl_3$) δ (ppm) 173.5 (C), 154.9 (CH), 138.3 (C), 128.7 (2 CH), 127.6 (CH), 127.6 (2 CH), 82.8 (C), 66.7 (C), 51.7 (CH_3), 45.8 (CH_2), 28.1 (CH_2), 21.2 (CH_3), 20.4 (CH_3), 9.2 (CH_3); IR (KBr) 3205 (w), 2877 (m), 1951 (w), 1747 (s), 1598 (s), 1456 (m), 1253 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 274 (2) $[M]^+$, 245 (2) $[M - C_2H_5]^+$, 215 (100) $[M - C_2H_3O_2]^+$, 183 (6) $[M - C_7H_7]^+$, 91 (58) $[C_7H_7]^+$; HR-MS (EI, 70 eV) calcd for $C_{16}H_{22}N_2O_2$ (M^+) 274.16813, found 274.16719.

Methyl 1,4-Dibenzyl-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5i). General procedure 4 was followed using **4i** (378 mg, 2.0 mmol). Forty-eight hour reaction time followed by column chromatography (Al_2O_3, EtOAc/pentane (10%), R_f 0.44) furnished **5i** (706 mg, quantitative) as a pale yellow oil.

^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 7.37−7.18 (m, 10H), 6.87 (s, 1H), 4.24 (d, ^2J = 15.1 Hz, 1H), 4.14 (d, ^2J = 15.1 Hz, 1H), 3.59 (s, 3H), 3.15 (d, ^2J = 12.8 Hz, 1H), 2.87 (d, ^2J = 12.8 Hz, 1H), 1.41 (s, 3H), 1.08 (s, 3H); ^{13}C{^{1}H} NMR (62.90 MHz, $CDCl_3$) δ (ppm) 172.7 (C), 154.7 (CH), 138.3 (C), 137.0 (C), 130.5 (2 CH), 128.7 (2 CH), 127.7 (2 CH), 127.6 (CH), 127.6 (2 CH), 126.3 (CH), 82.9 (C), 67.3 (C), 51.5 (CH_3), 45.8 (CH_2), 40.7 (CH_2), 20.9 (CH_3), 20.5 (CH_3); IR (KBr) 3029 (m), 2971 (m), 2947 (m), 1950 (w), 1877 (w), 1750 (s), 1718 (s), 1598 (s), 1495 (m), 1215 (br, s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 366 (1) $[M]^+$, 277 (16) $[M - C_2H_3O_2]^+$, 245 (100) $[M - C_7H_7]^+$, 91 (70) $[C_7H_7]^+$; HR-MS (EI, 70 eV) calcd for $C_{21}H_{24}N_2O_2$ (M^+) 366.18378, found 366.18473.

Methyl 1-Benzyl-4-isobutyl-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5j). General procedure 4 was followed using **4j** (310 mg, 2.0 mmol). After 48 h reaction time, **5j** (466 mg, 1.54 mmol, 77%) could be isolated as a pale yellow oil.

^{1}H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 7.38−7.29 (m, 5H), 6.78 (s, 1H), 4.18 (d, ^2J = 15.2 Hz, 1H), 4.09 (d, ^2J = 15.2 Hz,

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1H), 3.75 (s, 3H), 1.88 (m, 1H), 1.71 (dd, $^2J = 12.9$ Hz, $^3J = 6.8$ Hz, 1H), 1.59 (dd, $^2J = 12.9$ Hz, $^3J = 6.8$ Hz, 1H), 1.23 (s, 3H), 1.00 (s, 3H), 0.94 (d, $^3J = 6.6$ Hz, 3H), 0.85 (d, $^3J = 6.6$ Hz, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$) δ (ppm) 174.1 (C), 154.6 (CH), 138.4 (C), 128.7 (2 CH), 127.6 (2 CH), 127.6 (CH), 81.4 (C), 67.5 (C), 51.6 (CH_3), 45.8 (CH_2), 42.7 (CH_2), 25.1 (CH_3), 24.5 (CH), 22.6 (CH_3), 20.6 (CH_3), 20.0 (CH_3); IR (KBr) 3160 (w), 2950 (w), 2867 (w), 1747 (s), 1598 (s), 1454 (m), 1035 (s) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 302 (2) $[M]^+$, 287 (22) $[M - CH_3]^+$, 243 (68) $[M - C_2H_3O_2]^+$, 231 (18) $[M - C_5H_{11}]^+$, 211 (10) $[M - C_7H_7]^+$, 187 (20) $[M - C_6H_{11}O_2]^+$, 91 (100) $[C_7H_7]^+$; HR-MS (EI, 70 eV) calcd for $C_{18}H_{26}N_2O_2$ (M^+) 302.19943, found 302.19953.

Methyl 1-Benzyl-4-isopropyl-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (5k). General procedure 4 was followed using **4k** (282 mg, 2.0 mmol) and AgOAc (6.6 mg, 0.04 mmol, 2 mol %). After 4 weeks reaction time, **5k** (328 mg, 1.1 mmol, 57%) could be isolated as a yellow oil.

^1H NMR (250.13 MHz, $CDCl_3$) δ (ppm) 7.37−7.28 (m, 5H), 6.86 (s, 1H), 4.14 (d, $^2J = 14.6$ Hz, 1H), 4.08 (d, $^2J = 14.6$ Hz, 1H), 3.75 (s, 3H), 2.29 (hp, $^3J = 6.6$ Hz, 1H), 1.35 (s, 3H), 1.04 (s, 3H), 0.96 (d, $^3J = 6.6$ Hz, 3H), 0.89 (d, $^3J = 6.6$ Hz, 3H); $^{13}C\{^1H\}$ NMR (62.90 MHz, $CDCl_3$) δ (ppm) 174.0 (C), 155.2 (CH), 137.8 (C), 128.7 (2 CH), 128.1 (2 CH), 127.7 (CH), 85.5 (C), 66.3 (C), 51.4 (CH_3), 46.2 (CH_2), 32.8 (CH), 22.4 (CH_3), 19.3 (CH_3), 19.2 (CH_3), 17.3 (CH_3); IR (KBr) 3019 (w), 2821 (s), 1956 (w), 1747 (s), 1598 (m), 1454 (m), 1043 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 288 (4) $[M]^+$, 245 (100) $[M - C_3H_7]^+$, 229 (69) $[M - C_2H_3O_2]^+$, 197 (6) $[M - C_7H_7]^+$, 187 (19) $[M - C_5H_9O_2]^+$, 91 (78) $[C_7H_7]^+$; HR-MS (EI, 70 eV) calcd for $C_{17}H_{24}O_2N_2$ (M^+) 288.18378, found 288.18354.

Alternatively, **4k** (282 mg, 2.0 mmol), benzylamine (**7**) (220 μL, 214 mg, 2.0 mmol), acetone (**6**) (150 μL, 116 mg, 2.0 mmol), AgOAc (33.3 mg, 0.2 mmol, 10 mol %), and $MgSO_4$ (100 mg) were stirred in methanol (1 mL) for 2 weeks at room temperature. Water (15 mL) was added, and the resulting mixture was extracted with DCM (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to yield pure **5k** (578 mg, 2.0 mmol, quantitative).

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Supporting Information Available: General experimental methods and spectral data (^1H NMR and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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