

One-pot domino synthesis of polyvicinalamine monomers

Cem B. Kilic and Alpay Taralp

Abstract: Imidazole was generated in situ via a domino reaction between glyoxal, formaldehyde, and two units of aqueous ammonia. Aqueous bicarbonate and a carboxylic anhydride or dialkyl dicarbonate were added, yielding the corresponding *N,N'*-diacyl or *N,N'*-dicarbalkoxy-2-hydroxyimidazoline. A Bamberger ring cleavage ensued, affording *cis*-1,2-di(acetamido)ethene, *cis*-1,2-di(propylamido)ethene, *cis*-1,2-di(ethoxyamido)ethene, *cis*-1,2-di(*tert*-butoxyamido)ethene, or *cis*-1,2-di(benzamido)ethene as easily isolable solids. The convenience and generality offered by this one-pot approach implied a cost-effective route to the routine synthesis of oligo- and polyvicinalamine precursors.

Key words: Bamberger ring cleavage, domino reaction, one-pot reaction, multicomponent reaction, polyvicinalamine monomers.

Résumé : On a généré de l'imidazole par une réaction de type domino in situ entre le glyoxal, le formaldéhyde et deux unités d'ammoniac aqueux. L'addition de bicarbonate aqueux et d'un anhydride carboxylique ou d'un dicarbonate de dialcyle conduit à la formation de la *N,N'*-diacyl- ou *N,N'*-dicarbalkoxy-2-hydroxyimidazoline correspondante. Il s'ensuit une réaction de clivage de cycle de Bamberger qui permet d'isoler facilement le *cis*-1,2-di(acétamido)éthène, le *cis*-1,2-di(propylamido)éthène, le *cis*-1,2-di(éthoxyamido)éthène, le *cis*-1,2-di(*tert*-butoxyamido)éthène ou le *cis*-1,2-di(benzamido)éthène sous la forme de solides. La facilité et la généralité offerte par cette approche monotope implique une voie efficace du point de vue des coûts en vue de la synthèse de routine de précurseurs d'amines oligo- et polyvicinales.

Mots-clés : clivage de cycle de Bamberger, réaction de type domino, réaction monotope, réaction à plusieurs composants, amine vicinale.

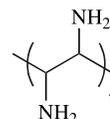
[Traduit par la Rédaction]

Introduction

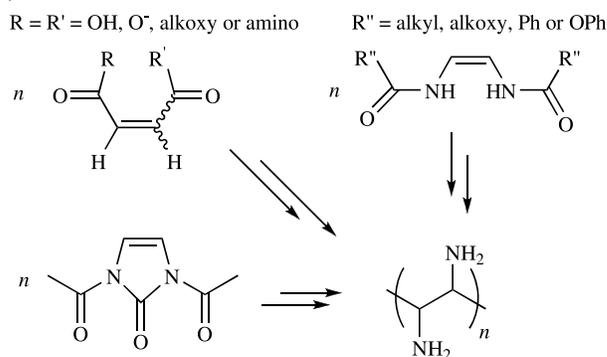
Polyamines have received much interest in view of their high amino group content, multi-interaction modes, facile tailorability, and widespread applicability in products ranging from commodity chemicals for pulp processing or water treatment to specialty chemicals intended for use in pharmacy and biotechnology.^{1–3}

Recently, oligo- and polyvicinalamines with an impressive 1:1 nitrogen–carbon ratio were prepared (Scheme 1). Of the three approaches portrayed (Scheme 2), the monomers utilized have been based on butenedioic acid, *cis*-1,2-diamidoethene, and 1,3-diacetyl-4-imidazolin-2-one.^{1–13} The use of commercial butenedioic acid-type monomers (Scheme 2, top left) introduces inconveniences related to halogenation, corrosion control, and waste management. The use of *cis*-1,2-diamidoethene monomers (Scheme 2, top right) permits a relatively simpler, greener industrial process. Still, neither approach has enabled the formation of high molecular weight polyvicinalamines.^{2–5} The polymerization of 1,3-diacetyl-4-imidazolin-2-one (Scheme 2, bottom left) has yielded comparatively higher molecular weight materials.^{2,4} This last monomer, a cyclic analogue of *cis*-1,2-di(acetamido)ethene (**1a**, entry 1 in Table 1), is

Scheme 1. Polyamine featuring a 1:1 nitrogen–carbon ratio.



Scheme 2. Monomers used to prepare oligo- and polyvicinalamines: butenedioic acid and derivatives (top, left), *cis*-1,2-diamidoethene (top, right), and 1,3-diacetyl-4-imidazolin-2-one (bottom, left).



Received 13 August 2010. Accepted 15 December 2010. Published on the NRC Research Press Web site at canjchem.nrc.ca on 25 March 2011.

C.B. Kilic and A. Taralp.¹ Faculty of Engineering and Natural Sciences, Sabanci University, Tuzla 34956 Istanbul, Turkey.

¹Corresponding author (e-mail: taralp@sabanciuniv.edu).

Table 1. Reaction of in situ-generated imidazole with activating agents in alkaline media (products: *cis*-1,2-di(acetamido)ethene (**1a**), *cis*-1,2-di(ethoxyamido)ethene (**2a**), *cis*-1,2-di(*tert*-butoxyamido)ethene (**3a**), *cis*-1,2-di(benzamido)ethene (**4a**), and *cis*-1,2-di(propylamido)ethene (**5a**)).

Entry	Acylating/alkoxyformylating agent	Product	Time (h)	Solvent	Yield ^a (%)	Yield ^b (%)
1			13	H ₂ O/EtOAc	35	53.8 (80) ^e
2			12	H ₂ O/EtOAc	22.4	34.5 (60) ^d
3			30	H ₂ O/1,4-Dioxane	28.7	44.1 ^e
4			12.5	H ₂ O/1,4-Dioxane	14.7	22.6 (10, 43) ^f
5			12	H ₂ O/EtOAc	39.2	60.3 ^e

^a Yields were calculated with respect to glyoxal as limiting reagent.

^b Yields with respect to in-situ-generated imidazole were estimated after determining a 65% yield by ¹H NMR. Parentheses indicate literature yields.

^c Literature yield with imidazole as starting material and limiting reagent.¹

^d Literature yield with imidazole as starting material and limiting reagent, and ethylchloroformate as ethoxyformylating agent.²

^e No literature preparation was available for comparative purposes.

^f Literature yields with imidazole as starting material and limiting reagent, and benzoyl chloride as benzoylating agent.^{2,10}

highly reactive by virtue of the ring structure, which limits steric clutter about the double bond, and the acetyl groups, which overcome limitations inherent to polymerizing 4-imidazolin-2-one.³ Still, the high hydrolytic stability of the polymeric intermediate formed demands harsh conditions to generate the free polyvicinalamine.³

Some other factors, which influence the production feasibility of these polyamines, include the cost and commercial availability of the starting materials. Whereas the butenedioic acid-based monomers are readily available, the *cis*-1,2-diamidoethene monomers are inevitably prepared using commercial imidazole. An even more inconvenient starting material, 1,3-diacetyl-4-imidazolin-2-one, is prepared from 4-imidazolin-2-one, a synthon that is commercially unavailable.⁵ Interestingly, the related monomer 1,3-diethoxy-4-imidazolin-2-one has been prepared directly from *cis*-1,2-di(ethoxyamido)ethene (**2a**, entry 2 in Table 1) by treatment with phosgene.⁴ As this route bypassed 4-imidazolin-2-one, it seemed reasonable to assume that a suitable source of imidazole, prepared very cost effectively, could serve as a raw material of both the *cis*-1,2-diamidoethene type monomers and heterocyclic variants such as 1,3-diacetyl-4-imidazolin-2-one. This prospect was also attractive in that it seemed extendable to the preparation and conversion of 4-substituted and 4,5-disubstituted imidazoles.

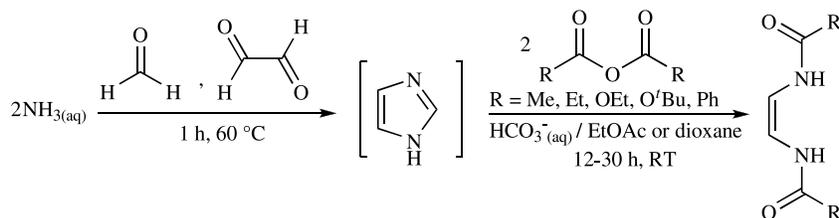
In this work, a simple approach was envisaged to generate and utilize imidazole, affording the *cis*-1,2-diamidoethene monomers. The rationale was to prepare imidazole in situ

via a domino synthesis,^{7,13,14} and to continue directly with a Bamberger reaction (Schemes 3 and 4).¹ As implied, a key advantage of this approach was to bypass the inconveniences normally associated with isolating imidazole.^{7,13} Integrating the two processes into a one-pot strategy appeared technically feasible, given that each reaction has traditionally been conducted in aqueous media. In a typical in-house procedure (Scheme 3), a small excess of ammonia and stoichiometric amounts of glyoxal and formaldehyde, were heated in a slightly oversized vessel, yielding imidazole. Unlike the classic 3 h domino synthesis,⁷ the generation of imidazole was restricted to 1 h; time-course trials confirmed that the yields of *cis*-1,2-di(acetamido)ethene (**1a**, entry 1 in Table 1) were not improved by further incubation. The conditions to achieve ring cleavage were subsequently established in the same pot by modifying the solvent system and temperature. The workup was facilitated by spontaneous crystallization or selective organic-phase partitioning of the *cis*-1,2-diamidoethene products. Recrystallization was conceivably optional, as the “crude” lyophilized products revealed a purity, which implied their suitability as monomers.^{1,2}

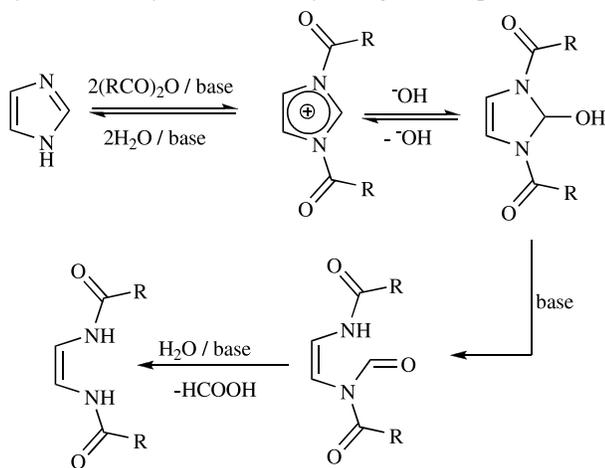
Results and discussion

The one-pot process proved easy to implement and amenable to a broad selection of acylating agents (**1–5**, Table 1). The yields, while modest, were offset by the extremely cheap starting materials and ease of product isolation. The

Scheme 3. One-pot domino reaction scheme to afford *cis*-1,2-di(alkylamido)ethene, *cis*-1,2-di(alkoxyamido)ethene, and *cis*-1,2-di(benzamido)ethene from commodity materials.



Scheme 4. Bamberger ring cleavage pathway in aqueous bicarbonate. Imidazole is activated via carboxylic anhydride or dialkyl dicarbonate.¹ The *N,N'*-diacyl or *N,N'*-dicarbalkoxy imidazolium species formed is attacked by hydroxide at the C-2 center, affording an *N,N'*-diacyl or *N,N'*-dicarbalkoxy-2-hydroxyimidazoline. Ring fission ensues, producing a *cis*-1,2-diamido-*N*-formylethene. Hydrolytic *N*-deformylation follows, yielding the end product.



facility of the overall process was best illustrated by the example of acetic anhydride (**1**, entry 1 in Table 1), which upon gradual addition smoothly afforded **1a** via spontaneous crystallization.¹ The process was readily upscaled to 30 L, further implying its industrial merit. The approach also served to confirm the general utility of acid anhydrides, as all work on the Bamberger reaction had been focused, until recently,¹ on the use of benzoyl chloride, alkyl and aryl chloroformates, and **2**.^{2,6,8–11} This validation was particularly encouraging, as one of the two reported attempts to prepare a *cis*-1,2-di(alkylamido)ethene, specifically **1a**, had failed using **1**.¹² Lastly, the stereo-electronic diversity among **1a–5a** (Table 1) was attractive, as it could potentially serve to extend the utility of this monomer class. For instance, a copolymer prepared from **1a**, **2a**, and **3a** could likely be prompted to selectively deblock under the appropriate conditions.

Prior studies^{6,9} on the Bamberger reaction provided a mechanistic basis to relate product yield to the conversion of a 2-hydroxyimidazoline intermediate. As shown in Scheme 4, ring fission is initially prompted by the stepwise *N,N'*-diacylation or *N,N'*-dicarbalkoxy formylation of imidazole in aqueous base, forming an activated imidazolium species. Hydroxide attack ensues at the C-2 carbon, reversibly forming a *N,N'*-diacyl or *N,N'*-dicarbalkoxy-2-hydroxyimidazoline. A general or specific base-catalyzed cleavage of the ring

follows, yielding a *cis*-1,2-diamido-*N*-formylethene. The formyl group is hydrolyzed via base catalysis, affording the *cis*-1,2-diamidoethene product. Hydrolytic pathways are also known to resist the activation of imidazole. These act to quench reagents and to hydrolyze any *N*-substituted and *N,N'*-disubstituted imidazoles. By probing the interaction of imidazole and **2** at low concentrations, Grace et al.⁶ described a kinetic scenario, characterizable by the rapid accumulation of 2-hydroxy-*N,N'*-dicarbalkoxyimidazoline, the slow cleavage of the ring, and the pH-dependent and typically rate-determining deformylation of the carbon at position C-2. As all reactants of the current study were utilized at much higher initial concentrations, it was safe to conclude that the *N,N'*-disubstituted 2-hydroxyimidazoline intermediate derived from each of **1–5** would be rapidly formed. In the mechanistic assessment of Grace et al.,⁶ it was also clear that given enough time, the yield of *cis*-1,2-di(ethoxyamido)ethene would not reflect the deformylation rate of *cis*-1,2-diethoxyamido-*N*-formylethene. Rather, it would reflect the committed conversion of 2-hydroxy-*N,N'*-dicarbalkoxyimidazoline to *cis*-1,2-diethoxyamido-*N*-formylethene. Thus, achieving a good yield ultimately rested on establishing an extended and sufficiently high steady-state concentration of the imidazoline, a task realized by discouraging hydrolytic deactivation and optimizing the availability of **2**. A similar kinetic view applied to the current work. Namely, the yield of each of **1a–5a** (Table 1) reflected the extent to which an effective and prolonged conversion of the corresponding *N,N'*-disubstituted 2-hydroxyimidazoline could be realized. Hence, the yield discrepancies amongst **1a–5a** not only reflected inherent stereoelectronic differences acting along the reaction coordinate, but presumably also some variations related to the addition of **1–5**. The literature yields (in parentheses in Table 1) were generally superior to the corresponding in-house process. No attempt was made to derive insight from this discrepancy, as the protocols differed notably.²

From a practical viewpoint, the yields were generally improved by both strong stirring, which served to disperse **1–5**, and by the moderately prolonged addition of sufficient **1–5**, which prompted the steady *N,N'*-diacylation or *N,N'*-dicarbalkoxylation of imidazole (Scheme 4). While the influence of pH on the course of the reaction had not been systematically characterized at large reactant concentrations, the Bamberger reaction was reported to proceed best within the pH range of 6–7.⁶ Increasing the alkalinity further was discouraged, as the half-life of the *N,N'*-diacyl or *N,N'*-dicarbalkoxy imidazolium species would drop accordingly, detracting from the accumulation and turnover of the corresponding 2-hydroxyimidazoline. Still, the findings obtained

herein using alkaline bicarbonate implied a rather flexible working pH range of reaction.

As a final point, the elusive *cis*-1,2-di(formamido)ethene was targeted in view of its potential to serve as an easily polymerizable monomer.¹ Just as with prior attempts, however, no product was isolated when formic acetic anhydride was added to the in situ-generated imidazole or to commercially produced imidazole as per the established method.¹ The fact that imidazole was recovered unchanged was attributed to the high accessibility and electropositive nature of the formyl carbonyl center, which presumably served to speed the hydrolytic deactivation of reagent and formylated imidazole species.

To summarize, several *cis*-1,2-diamidoethene monomers were prepared by manipulating glyoxal, formaldehyde, ammonia, and an acylating agent in one pot. The process precluded the purification of intermediates, the deployment of relatively expensive or volatile compounds like imidazole and chloroformate, and any laborious workup. The fact that an industrially applicable end product was prepared and readily isolable, following a four-component transformation in the presence of many potentially interfering by-products,⁷ further attested to the facility and robustness of this strategy. Finally, whereas *cis*-1,2-diamidoethene can serve as a monomer, this class of compound may also be converted to the corresponding *N,N'*-disubstituted 4-imidazolin-2-one heterocycle,⁴ which is known to have a much greater propensity to polymerize.³ All in all, it would appear that the cost efficiency and conveniences imparted by this one-pot approach could promote the routine preparation and use of oligo- and polyvicinalamines.

Experimental

Technical grade starting materials were obtained from local suppliers and were used without further purification.

Typical experimental procedure

To a stirred solution of ammonium hydroxide (6.0 g, 22–25 wt%), a mixture of glyoxal (4.35 g, 30.0 mmol, 40 wt%) and formaldehyde (2.25 mL, 30.2 mmol, 37 wt%) was cautiously added. The mixture was allowed to stir (60 °C, 1 h), generating imidazole. Subsequently, distilled water (150.0 mL), ethylacetate (30.0 mL), and sodium bicarbonate (25.0 g) were added to the reaction. Acetic anhydride (12.0 mL, 127.0 mmol, 4.23 equiv with respect to glyoxal) was slowly added (30 min) under vigorous stirring during which time effervescence was noted. The reaction vessel was lightly capped after **1** was fully added and stirring was continued (13 h, room temperature (RT)) to promote full de-formylation. The precipitated solid was recovered by filtration, washed with distilled water (3 × 5.0 mL), optionally triturated in distilled water (20.0 mL, 80 °C, 15–30 min), and lyophilized to yield **1a** (1.50 g, 35% with respect to glyoxal) as a white solid. Di-*tert*-butyl dicarbonate (**3**) was gently warmed prior to use and administered dropwise as in the case of acetic anhydride. Unlike **1–3** and **5**, benzoic anhydride (**4**) was finely pulverized and added in one shot. For **3a** and **4a**, 1,4-dioxane (75.0 mL) was used in place of ethylacetate (Entries 3–4). Precipitation of **4a** (Entry 4) was facilitated by adding water (250 mL) during the workup.

Product **5a** (Entry 5) was directly isolated by evaporating the ethylacetate layer. To ascertain the in situ yield of imidazole, an aliquot of the domino reaction (48.0 μL) was dissolved in deuterium oxide (600 μL) spiked with sodium acetate (24.0 μg). The sample was immediately analyzed using ¹H NMR (RT, D₂O/DHO presaturation, 10 s interpulse delay, and 256 scans). The signal corresponding to the three C–H protons of imidazole was compared with the three protons of acetate, permitting a yield calculation of the former compound.

Parameters used for characterization

NMR: Inova 500; ATR-FTIR: Bruker Equinox 55; GC–MS: gas chromatography, Agilent 6890N; GC column: J&W, DB5, 30 m, i.d. = 0.25 mm; film thickness: 0.25 μm; carrier gas: He; injection: 50 ng/1 μL MeOH; injection temp.: 270 °C; aux. temp.: 240 °C; temp. progr.: 100/5–5–260; mass spectrometry: Sensi-TOF, Five Technologies, Munich; mass range: 40–500 amu; ionization energy: 70 eV; DSC: Netzsch 204 Phoenix; temp. ramp rate: 5 K/min; atmosphere: N₂. A chemical shift of 2.5 ppm (¹H NMR) and 39.4 ppm (¹³C NMR) was applied to reference DMSO-*d*₆.¹⁵ The melting onset temperature (*T*_{onset}) was estimated from the DSC profile as per ASTM standard test procedure E794.¹⁶ The peak melting temperature (*T*_m) was obtained by direct inspection. Both values have been expressed for clarity. In **1a–5a**, the TLC runs showed one spot under UV light. All GC–MS profiles yielded one peak.

Entry 1

*R*_f: 0.06 (EtOAc); mp (recrys. EtOH): *T*_{onset} = 134.8 °C, *T*_m = 136.3 °C, lit. value¹ not reported. IR (neat) *v*: 3301 (w), 3211 (w), 3051 (w), 1708 (w), 1676 (m), 1637 (m), 1560 (m), 1356 (m), 1274 (m), 1164 (s), 1039 (m), 997 (m), 744 (m), 668 (s). ¹H NMR (500 MHz, DMSO-*d*₆) *δ*: 1.95 (s, 3H), 5.99 (m, 1H), 9.27 (d, 1H). ¹³C NMR (125.725 MHz, DMSO-*d*₆) *δ*: 22.61, 105.04, 166.13. GC–MS *m/e*: 142 M⁺. MS (C₆H₁₀N₂O₂) calcd: 142.16; found: 142.09. Anal. calcd: C 50.69, H 7.09, N 19.71; found: C 48.61, H 7.25, N 18.60.

Entry 2

*R*_f: 0.58 (EtOAc); mp (recrys. EtOH): *T*_{onset} = 141.3 °C, *T*_m = 143.7 °C (lit.¹¹ mp 139–141 °C). IR (neat) *v*: 3338 (w), 3316 (w), 3229 (w), 2976 (w), 1724 (m), 1668 (m), 1525 (s), 1455 (m), 1367 (m), 1308 (m), 1241 (s), 1149 (s), 1081 (s), 870 (m), 765 (m), 718 (s), 675 (m). ¹H NMR (500 MHz, DMSO-*d*₆) *δ*: 1.19 (t, 3H), 4.06 (q, 2H), 5.69 (m, 1H), 8.78 (d, 1H). ¹³C NMR (125.725 MHz, DMSO-*d*₆) *δ*: 14.31, 60.38, 105.24, 153.18. GC–MS *m/e*: 202 M⁺. MS (C₈H₁₄N₂O₄) calcd: 202.21; found: 202.12. Anal. calcd: C 47.52, H 6.98, N 13.85; found: C 47.23, H 6.76; N 13.62.

Entry 3

*R*_f: 0.66 (EtOAc); mp (recrys. EtOH): *T*_{onset} = 221.9 °C, *T*_m = 223.7 °C. IR (neat) *v*: 3340 (w), 3255 (w), 3226 (w), 2975 (w), 1723 (m), 1692 (s), 1525 (s), 1454 (w), 1367 (m), 1307 (m), 1239 (s), 1146 (s), 1080 (s), 869 (m), 772 (m), 717 (s), 676 (m). ¹H NMR (500 MHz, DMSO-*d*₆) *δ*: 1.41 (s, 9H), 5.61 (m, 1H), 8.59 (d, 1H). ¹³C NMR (125.725 MHz, DMSO-*d*₆) *δ*: 27.92, 78.94, 104.75, 152.29.

GC-MS *m/e*: 258 M⁺. MS (C₁₂H₂₂N₂O₄) calcd: 258.31; found: 258.23. Anal. calcd: C 55.80, H 8.58, N 10.84; found: C 54.25, H 3.78, N 7.18.

Entry 4

*R*_f: 0.48 (EtOAc); mp (recrys. EtOH): *T*_{onset} = 204.7 °C, *T*_m = 207.8 °C (lit.¹¹ mp 212–213 °C). IR (neat) *v*: 3322 (w), 3265 (w), 3057 (w), 1697 (m), 1670 (m), 1619 (m), 1515 (s), 1487 (s), 1316 (m), 1275 (s), 1259 (s), 1175 (s), 1147 (m), 1075 (w), 921 (m), 802 (m), 693 (s). ¹H NMR (500 MHz, DMSO-*d*₆) *δ*: 6.40 (m, 1H), 7.52–7.64 (m, 2H), 7.89–7.94 (m, 3H), 10.10 (d, 1H). ¹³C NMR (125.725 MHz, DMSO-*d*₆) *δ*: 106.69, 127.17, 128.42, 131.94, 133.79, 163.81. GC-MS *m/e*: 266 M⁺. MS (C₁₆H₁₄N₂O₂) calcd: 266.29; found: 265.88. Anal. calcd: C 72.17, H 5.30, N 10.52; found: C 53.04, H 7.53, N 15.32.

Entry 5

*R*_f: 0.23 (EtOAc); mp (recrys. EtOH): *T*_{onset} = 138.4 °C, *T*_m = 139.6 °C. IR (neat) *v*: 3316 (w), 3199 (w), 2982 (w), 1706 (m), 1687 (m), 1635 (m), 1549 (s), 1507 (s), 1457 (s), 1420 (m), 1375 (m), 1280 (w), 1239 (m), 1202 (s), 1163 (s), 1085 (m), 1029 (m), 940 (w), 758 (s), 646 (m). ¹H NMR (500 MHz, DMSO-*d*₆) *δ*: 1.04 (t, 3H), 2.12 (q, 2H), 6.00 (m, 1H), 9.26 (d, 1H). ¹³C NMR (125.725 MHz, DMSO-*d*₆) *δ*: 9.41, 28.46, 104.99, 169.86. GC-MS *m/e*: 170 M⁺. MS (C₈H₁₄N₂O₂) calcd: 170.21; found: 170.13. Anal. calcd: C 56.45, H 8.29, N 16.46; found: C 54.49, H 7.87, N 10.19.

Acknowledgments

The authors acknowledge B. Yıldız of Sabancı University (SU), Istanbul, Turkey, and M. Wiesheu, A. Friess, and M. Çölhan of the Technical University of Munich (TUM) for technical help; H. Parlar of TUM for supporting the MS tests and elemental analyses, M. Manyas of the SU Information Center for procuring literature, and C. Ow Yang of SU and E. Alberico of the Consiglio Nazionale Delle Ricerche (CNR)-Sassari, Italy, for comments.

References

- (1) Chang, H. T.; Charmot, D.; Zard, S. W. O. Patent 2005/041900, 2005.
- (2) Dyllick-Brenzinger, R.; Steuerle, U.; Braig, V. W. O. Patent 2004/013207, 2004.
- (3) Klapper, M.; Hamciuc, C.; Dyllick-Brenzinger, R.; Müllen, K. *Angew. Chem. Int. Ed.* **2003** *42* (38), 4687. doi:10.1002/anie.200351500.
- (4) Kundu, N. R. Synthesis, Characterization & Chemical Modification of a Novel Cationic Polyelectrolyte Poly(methylene amine). Ph.D. Thesis, Johannes Gutenberg-Universität Mainz, Germany, 2007.
- (5) Haines, D. R.; Leonard, N. J.; Wiemer, D. F. *J. Org. Chem.* **1982** *47* (3), 474. doi:10.1021/jo00342a020.
- (6) Grace, M. E.; Loosemore, M. J.; Semmel, M. L.; Pratt, R. F. *J. Am. Chem. Soc.* **1980** *102* (22), 6784. doi:10.1021/ja00542a020.
- (7) Mesch, W. US Patent 4,719,309, 1988.
- (8) Bamberger, E. *Justus Liebigs Ann.* **1893** *273*, 342–363, 267–269.
- (9) Loosemore, M. J.; Pratt, R. F. *FEBS Lett.* **1976** *72* (1), 155. doi:10.1016/0014-5793(76)80834-4.
- (10) Morkovnik, A. S.; Khrustalev, V. N. *Russ. Chem. Bull.* **1998** *47* (8), 1550. doi:10.1007/BF02495608.
- (11) Babad, E.; Ben-Ishai, D. *J. Heterocycl. Chem.* **1969** *6* (2), 235. doi:10.1002/jhet.5570060215.
- (12) Hoffmann, K. *Imidazole and Its Derivatives*; Interscience Publishers: New York, 1953; Part I, p 48.
- (13) Arduengo, A. J.; Gentry, F. P.; Taverkera, P. K.; Simmons, H. E. US Patent 6,177,575, 2001.
- (14) As described previously (Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136), a domino reaction entails the formation of at least two bonds with the proviso that the reaction conditions are not altered, additional reagents are not added, and at least one transformation yields a functionality that also enters the reaction.
- (15) Macomber, R. S. *A Complete Introduction to Modern NMR Spectroscopy*; Wiley: New York, 1998.
- (16) American Society of Testing and Materials. *ASTM E754, Standard Test Methods for Melting and Crystallization Temperatures by DSC*; Annual Book of ASTM Standards, 14.02; ASTM International: West Conshohocken, PA, 1994.