Pyridine-Mediated Synthesis of 1,3-Diazetidin-2-ones (Aza-β-lactams): Novel Investigations on Isocyanate–Carbodiimde Reaction

Abdolali Alizadeh,*[a] Nasrin Zohreh,[a] Ghasem Oskueyan,[a] Long-Guan Zhu[b]

[a] Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran
Fax +98(21)88006544; E-mail: abdol_alizad@yahoo.com; E-mail: aalizadeh@modares.ac.ir

[b] Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. of China

Received 16 May 2011

Abstract: The reported cycloaddition reaction of isocyanates and symmetric carbodiimides is reinvestigated in the presence of pyridine. The Huisgen zwitterion generated by the 1:1 addition of pyridine to arylsulfonyl isocyanate is trapped by dialkyl carbodiimide to obtain symmetrical 1,3-diazetidin-2-ones via a novel intramolecular rearrangement.

Key words: 1,3-diazetidin-2-one, aza-β-lactam, carbodiimide, arylsulfonyl isocyanate, pyridine

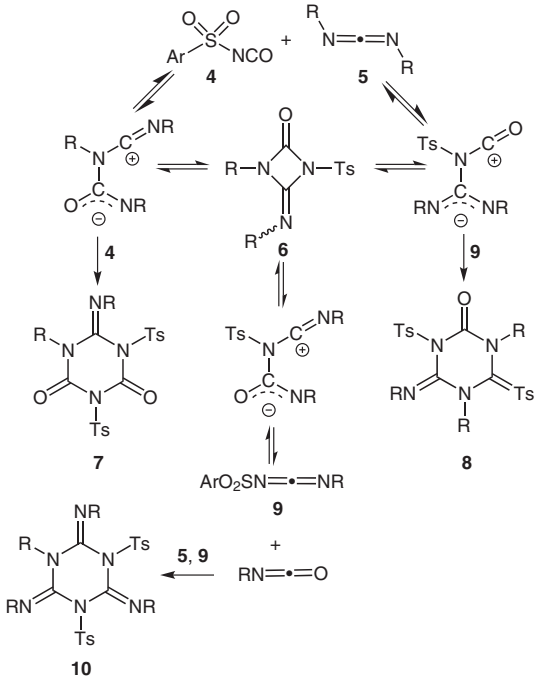
1,3-Diazetidin-2-ones exhibit activities including antibacterial[1] and anti-inflammatory[2] activity. Recently, they have been found to be potent serine peptidase, transpeptidase, and β-lactamase enzyme inhibitors.[1,3,4] 1,3-Diazetidinone derivatives are also used in polyester polyurethane resins which offer good abrasion resistance[5] and heat resistance.[6]

Despite their applications, to our knowledge there are only a few methods for the preparation of 1,3-diazetidin-2-ones; these include carbonylation of diaziridines by Pd or Co complexes,[7] addition of isocyanates to imines preferably activated with an electron-donating group such as OMe (imino ethers),[8] photolytic reaction of chromium carbene complexes with azobenzenes,[9] photolysis of the pyrimidin-2-one derivatives,[1,10] and base transformation of *N*-(chlorocarbonyl)guanidine.[11]

The [2+2]-cycloaddition reaction of heterocumulenes, such as carbodiimides, isocyanates, and isothiocyanates, is well-known for the preparation of 1,3-diazetidinones.[12] These studies began in 1957;[13] then, in 1962, Neumann and Fischer investigated the reaction of different types of aryl isocyanates and symmetrical diaryl or dialkyl carbodiimides and obtained unsymmetrical carbodiimides via 1,3-diazetidine-2-one intermediates under thermal conditions.[14] Finally, Sayigh[15] and Ulrich[16] identified 1,3-diazetidine-2-one **1** as the main product of the cycloaddition reaction of arylisocyanates **2** and carbodiimides **3** (Scheme 1).[17] They also investigated the regioselectivity of the reaction in the case of unsymmetrical carbodiimides and reported that steric hindrance and electronic effects could influence the product distribution.[18] In later studies it became evident that a considerably more complex reaction pattern emerges in the reaction of dialkyl carbodiimide with arylsulfonyl isocyanates.

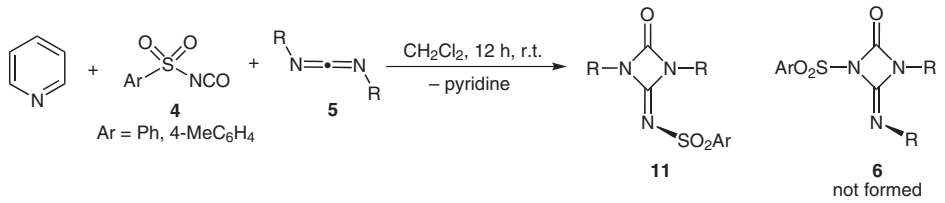
Scheme 1 The reaction of aryl isocyanate and carbodiimides

Based on the studies of Ulrich, the polar cycloaddition reaction of arylsulfonyl isocyanates **4** with dialkyl carbodiimides **5** gave rise to three six-membered ring cycloadducts **7**, **8**, and **10**. However, it is important to note that 1,3-diazetidinone intermediate **6** was not isolated, but simultaneous occurrence of the exchange reaction to form **7** and especially product **8** and **10** support the intermediacy of **6**.[19] This evidence was also confirmed by IR analysis of the reaction mixture at the beginning of the reaction (Scheme 2).[19,20]



Scheme 2 The reaction of arylsulfonyl isocyanate and dialkyl carbodiimde

SYNLETT 2011, No. 17, pp 2491–2494
Advanced online publication: 22.09.2011
DOI: 10.1055/s-0030-1260327; Art ID: D14711ST



Scheme 3 Synthesis N^1-(1,3-alkyl-4-oxo-1,3-diazetan-2-yliden)arylsulfonamides(4-arylimmino-1,3-diazetidine-2-ones)

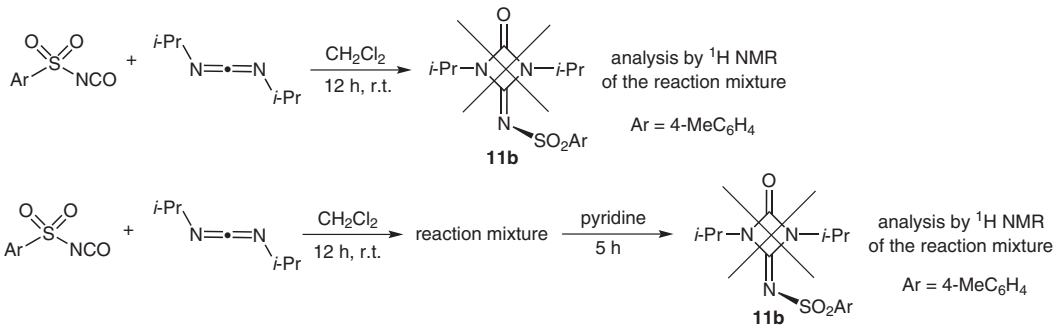
Cognizant of the potential synthetic interest and pharmacological activities of 1,3-diazetidinone and also considering the above history of the cycloaddition reaction of dialkyl carbodiimide and isocyanates, we decided to apply pyridine as a reagent in this reaction to prevent the further cyclization toward heterocyclic compound **7**, **8**, and **10** and permit isolation and characterization of the symmetrical 1,3-diazetidinone **11**.

Thus, in a continuation of our efforts directed toward the synthesis of N-containing heterocycles,[21] dialkylcarbodiimide **5** was subjected to reaction with arylsulfonyl isocyanate **4** in the presence of an equimolar amount of pyridine. The reaction proceeded smoothly in CH_2Cl_2 at room temperature for 12 hours. As outlined in Scheme 3, surprisingly, despite our expectation of a [2+2] product from this reaction, symmetrical 1,3-diazetidine-2-one **11** was obtained instead of unsymmetrical 1,3-diazetidine-2-one **6**.[22]

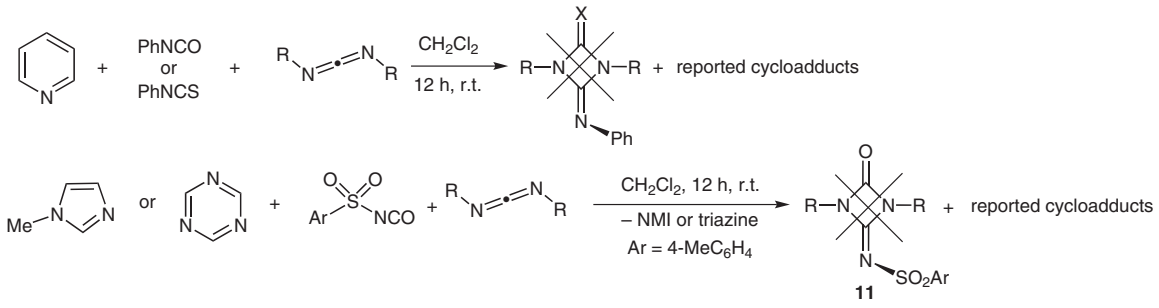
To evaluate the vital rule of pyridine in the formation of symmetrical 1,3-diazetidine-2-one **11**, two different reactions were designed and performed under conditions similar to the initial reaction. Firstly, the reaction of *p*-toluenesulfonyl isocyanate and diisopropyl carbdiimide was performed without pyridine for 12 hours. In the other experiment, the reaction of *p*-toluenesulfonyl isocyanate and diisopropyl carbdiiimde after 12 hours was subjected to the equivalent amount of pyridine for 5 hours. Both of the reaction mixtures were analyzed by ^{1}H NMR spectroscopy. As expected, product 1,3-diazetidine-2-one **11b** was not present, even in trace amounts (Scheme 4).

In an attempt to extend the scope of this conversion, we examined phenyl isocyanate and phenyl isothiocyanate instead of arylsulfonyl isocyanate in the above reaction. Unfortunately, no desired product was obtained, and the products were similar to the reported products for the pyridine-free reactions.[23] We also applied other aromatic N-heterocycles such as *N*-methyl imidazole and triazine to evaluate their role compared to the pyridine (Scheme 5). It was found that neither led to production of the desired 1,3-diazetidin-2-one **11**, and again the products were similar to the reported classic reactions.[12–20] All of our results are summarized in Table 1.

The structures of products were elucidated from their elemental analysis, MS, IR, and high-field ^{1}H and ^{13}C NMR spectra as described for **11a**. However, the mass spectrum of **11a** did not display a molecular ion peak at *m/z* = 403 but the ion peak at *m/z* = 322 showed the loss of the cyclohexyl group in the first fragmentation. In the IR spectrum



Scheme 4 Reactions that confirmed the role of pyridine for synthesis of 1,3-diazetidin-2-ones **11**

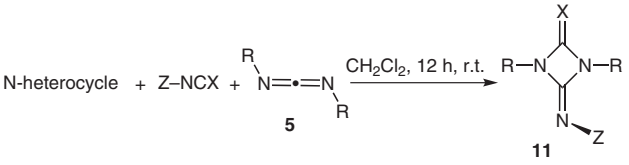


Scheme 5

of **11a**, two absorption bands at 1866 and 1640 cm^{-1}, related to C=O and C=N stretching frequencies, clearly indicated the most significant functional groups of the four-membered ring.

In the ^1H NMR spectrum of **11a**, 20 hydrogens of two chemically equivalent cyclohexyl exhibited signals between δ = 1.09–1.97 ppm. This fact is more clear for compound **11b** where all four chemically equivalent methyl groups of the isopropyl substituents appear as a 12-proton doublet at δ = 1.34 ppm ($^3J_{HH}$ = 6.6 Hz). A sharp singlet signal at δ = 2.45 ppm arises from the aromatic methyl group in **11a**. The most important signal of compound **11a** is the CH of the two chemically equivalent cyclohexyl groups which appears as a broad resonance at δ = 3.68 ppm. The aromatic hydrogens give characteristic signals in the aromatic region. The ^{13}C NMR spectrum of **11a** showed 11 distinct signals in agreement with the product structure. Finally, the structure of **11a** was further confirmed by a single-crystal X-ray diffraction (Figure 1).

Table 1 All results for Reactions of Isocyanates and Dialkyl Carbodiimide in the Presence of Aromatic N-Heterocycles



Entry	N-heterocycle	Product	Z	X	R	Yield (%)
1	pyridine	**11a**	4-$MeC_6H_4SO_2$	O	C_6H_{11}	42
2	pyridine	**11b**	4-$MeC_6H_4SO_2$	O	*i*-Pr	40
3	pyridine	**11c**	$PhSO_2$	O	C_6H_{11}	46
4	pyridine	**11d**	$PhSO_2$	O	*i*-Pr	45
5	NMI	–	4-$MeC_6H_4SO_2$	O	*i*-Pr	–
6	1,3,5-triazine	–	4-$MeC_6H_4SO_2$	O	*i*-Pr	–
7	pyridine	–	Ph	S	*i*-Pr	–
8	pyridine	–	Ph	O	*i*-Pr	–
9	NMI	–	Ph	S	*i*-Pr	–
10	NMI	–	Ph	O	*i*-Pr	–
11	1,3,5-triazine	–	Ph	S	*i*-Pr	–
12	1,3,5-triazine	–	Ph	O	*i*-Pr	–

Although no detailed mechanistic studies have been carried out at this point, our postulated reaction pathway is shown in Scheme 6. No doubt, the first step involves nucleophilic addition of pyridine to the highly reactive arylsulfonyl isocyanate **4** to produce Huisgen zwitterion **12**.[24] Subsequent trapping of dipole **12** by dialkyl carbodiimide **5** furnishes new pyridine-arylsulfonyl isocyanate–dialkyl carbodiimide zwitterion **13**. Presumably, since the nitrogen of NSO_2Ar group could stabilize the negative charge more easily than NR, resulting from the electron-withdrawing property of the $ArSO_2$, a four-center intramolecular rearrangement converts intermediate **13** into new zwitterion **14**. Finally, intramolecular ring-closure reaction followed by loss of pyridine affords the 4-imino-1,3-dizaetidin-2-one **11** derivatives.

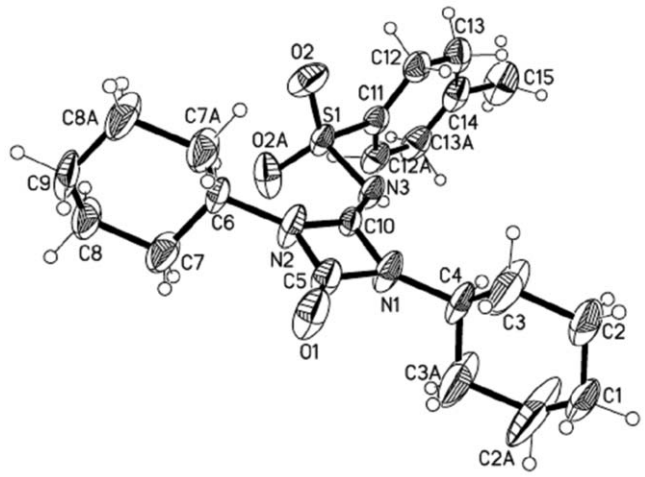
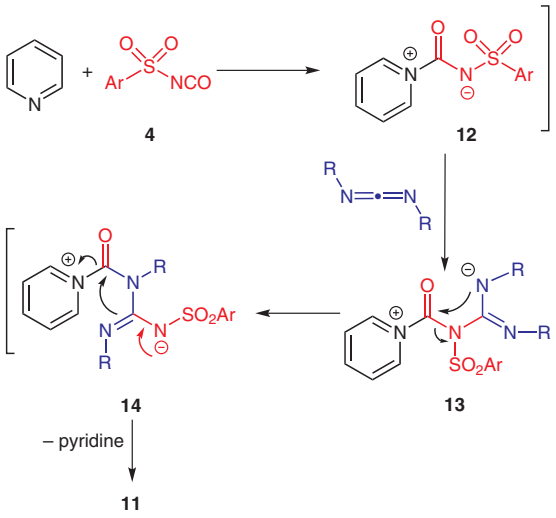


Figure 1 ORTEP diagram of **11a**



Scheme 6 Proposed mechanism for the mentioned reaction

In conclusion, we have presented a novel and unprecedented one-pot synthesis of symmetrical 4-imino-1,3-diazetidin-2-ones from the reaction of arylsulfonyl isocyanates and dialkyl carbodiimides in the presence of pyridine. Pyridine has been found to be a vital reagent as, without it, the reported cycloadducts are formed. Although the yields are relatively low, readily available and inexpensive starting materials, simple and mild reaction conditions, and simple purification as well as potential synthetic and pharmacological interest of the products make the present procedure an interesting alternative to the other approaches.

References and Notes

(1) Chandrakala, P. S.; Katz, A. K.; Carrell, H. L.; Sailaja, P. R.; Podile, A. R.; Nangia, A.; Desinaju, G. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2597.

(2) (a) Brehme, R.; Stroede, B.; Becker, H.; Foellmer, U.; Klemann, A.; Bohrisch, J.; Gruendemann, E. DD 221735, **1985**; *Chem. Abstr.* **1986**, *104*, 88516x. (b) Alpaegiani, M.; Perrone, E.; Orezi, P.; Carminati, P.; Cassinelli, G. DE 3820420, **1988**; *Chem. Abstr.* **1989**, *111*, 39093t.

(3) Aoyama, Y.; Uenaka, M.; Konoike, T.; Hayasaki-Kajiwara, Y.; Nayac, N.; Nakajima, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1691.

(4) (a) Nangia, A. *Proc. Indian Acad. Sci., Chem. Sci.* **1993**, *105*, 131. (b) Nangia, A.; Chandrakala, P. S.; Balaramakrishna, M. V.; Latha, T. V. A. *J. Mol. Struct.: THEOCHEM* **1995**, *343*, 157. (c) Nangia, A.; Chandrakala, P. S. *Tetrahedron Lett.* **1995**, *42*, 7771.

(5) Michels, E.; Wecher, D. DE 3939698, **1991**; *Chem. Abstr.* **1991**, *115*, 2092979.

(6) (a) Nishikawa, A. JP 0185215, **1989**; *Chem. Abstr.* **1989**, *111*, 175463r. (b) Nishikawa, A.; Koyama, T.; Asano, H. JP 245519, **1990**; *Chem. Abstr.* **1990**, *113*, 191328.

(7) Alper, H.; Delledonne, D.; Kameyama, M.; Roberto, D. *Organometallics* **1990**, *9*, 762.

(8) Aue, D. H.; Thomas, D. *J. Org. Chem.* **1975**, *40*, 2356.

(9) (a) Hegedus, L. S.; Lundmark, B. R. *J. Chem. Soc.* **1989**, *111*, 9194. (b) Hegedus, L. S.; Kramer, A. *Organometallics* **1984**, *3*, 1263.

(10) (a) Nishio, T.; Kato, A.; Kashima, C.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1980**, 607. (b) Nishio, T.; Nakajima, N.; Kashima, C.; Omote, Y. *Heterocycles* **1983**, *20*, 849.

(11) Richter, R.; Ulrich, H. *J. Org. Chem.* **1981**, *46*, 3011.

(12) Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*; Academic Press: New York, **1967**.

(13) Hofmann, R.; Schmidt, E.; Reichle, A.; Moosmuller, F. DE 1012601, **1957**; *Chem. Abstr.* **1959**, *53*, 19892g.

(14) Neumann, W.; Fischer, P. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 621; *Angew. Chem.* **1962**, *74*, 801.

(15) Farrissejeyr, W. J.; Ricciardai, R. J.; Sayigh, A. A. R. *J. Org. Chem.* **1968**, *33*, 1933.

(16) Ulrich, H. *Acc. Chem. Res.* **1969**, *2*, 186.

(17) (a) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457. (b) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589.

(18) (a) Richer, R.; Tucker, B.; Ulrich, H. *J. Org. Chem.* **1983**, *48*, 1694. (b) Ulrich, H.; Richer, R.; Tucker, B. *J. Heterocycl. Chem.* **1987**, *24*, 1121.

(19) Ulrich, H.; Tucker, B.; Stuber, F. A.; Sayigh, A. A. R. *J. Org. Chem.* **1969**, *34*, 2251.

(20) Ulrich, H.; Tucker, B.; Sayigh, A. A. R. *J. Am. Chem. Soc.* **1968**, *90*, 528.

(21) (a) Zohreh, N.; Alizadeh, A.; Bijanzadeh, H. R.; Zhu, L. G. *J. Comb. Chem.* **2010**, *12*, 497. (b) Alizadeh, A.; Noaparast, Z.; Sabahnoo, H.; Zohreh, N. *Synlett* **2010**, 1469. (c) Alizadeh, A.; Sabahnoo, H.; Noaparast, Z.; Zohreh, N.; Mikaeili, A. *Synlett* **2010**, 1854. (d) Alizadeh, A.; Zohreh, N. *Synlett* **2009**, 2146. (e) Alizadeh, A.; Zohreh, N.; Zhu, L. G. *Tetrahedron* **2009**, *65*, 2684.

(22) To a magnetically stirred solution of pyridine (160 mg, 2 mmol) and *p*-toluenesulfonyl isocyanate (400 mg, 2 mmol) in CH_2Cl_2 (5 mL) was added dicyclohexyl carbodiimide (410 mg, 2 mmol) in CH_2Cl_2 (2mL). The reaction mixture was stirred for 12 h in r.t. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (Merck 230–240 mesh) using a hexane–EtOAc (20:1) mixture as eluent. The product was recrystallized from Et_2O to obtain product **11a** as colorless crystals, mp 110–112 °C, 0.17 g, yield 42%. IR (KBr): ν_{max} = 1866 (C=O), 1648 (C=N), 1532 and 1439 (Ar), 1317 and 1151 (SO_2) cm^{-1}. Anal. Calcd (%) for $C_{21}H_{29}N_3O_3S$ (403.53): C, 62.51; H, 7.24; N, 10.41. Found: C, 62.55; H, 7.25; N, 10.42%. MS (EI, 70 eV): *m/z* (%) = 322 (88), 279 (14), 248 (21), 220 (19), 197 (28), 155 (66), 123 (17), 91 (100), 69 (15), 55 (43), 41 (7). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.09–1.96 (20 H, m, 20 H of 2 Cy), 2.45 (Me), 3.68 (2 H, br, 2 NCH), 7.33 (2 H, d, $^3J_{HH}$ = 7.8 Hz, 2 CH of Ph), 7.85 (2 H, d, $^3J_{HH}$ = 7.8 Hz, 2 CH of Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.55 (Me), 25.01 (2 CH_2), 25.18 (4 CH_2), 30.89 (4 CH_2), 54.65 (2 NCH), 126.74 (2 CH of Ph), 129.49 (2 CH of Ph), 138.55 (C_{ipso}-SO_2), 143.65 (C_{ipso}-Me), 154.88 (C=O), 157.05 (C=N).

Crystal Data for 11a

$C_{21}H_{33}N_3O_3S$ (CCDC 824721): M_W = 407.57, orthorhombic, space group 2*ac*, *a* = 21.8645 (18) Å, *b* = 9.7928 (9) Å, *c* = 10.0106 (9) Å, *α* = 90.00, *β* = 90.00, *γ* = 90.00, *V* = 2143.4 (3) Å^3, *Z* = 4, D_c = 1.263 mg/m^3, *F*(000) = 880, crystal dimension 0.26 × 0.18 × 0.07 mm, radiation, Mo Kα (*λ* = 0.71073 Å), 1.86 ≤ 2θ ≤ 25.00, intensity data were collected at 298 (2) K with a Bruker APEX area-detector diffractometer, and employing *ω*/2θ scanning technique, in the range of –21 ≤ h ≤ 26, –11 ≤ k ≤ 11, –9 ≤ l ≤ 11; the structure was solved by a direct method, all nonhydrogen atoms were positioned and anisotropic thermal parameters refined from 2014 observed reflections with *R* (into) = 0.1497 by a full-matrix least-squares technique converged to *R* = 0.1334 and *R*aw = 0.3306 [I > 2 σ(I)].

Compound 11c

Colorless crystals, mp 109–111 °C, 0.18 g, yield 46%. IR (KBr): ν_{max} = 1874 (C=O), 1659 (C=N), 1532 and 1439 (Ar), 1363 and 1150 (SO_2) cm^{-1}. Anal. Calcd (%) for $C_{20}H_{27}N_3O_3S$ (389.51): C, 61.67; H, 6.99; N, 10.79. Found: C, 61.66; H, 6.71; N, 10.82. MS (EI, 70 eV): *m/z* (%) = 389 (2) [M$^+$], 368 (18), 313 (21), 292 (26), 240 (37), 197 (22), 155 (87), 111 (57), 91 (87), 57 (100), 43 (54). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.12–1.96 (20 H, m, 20 H of Cy), 3.68 (2 H, br, 2 NCH), 7.54 (2 H, t, $^3J_{HH}$ = 7.4 Hz, 2 CH of Ph), 7.61 (1 H, t, $^3J_{HH}$ = 7.1 Hz, CH of Ph), 7.97 (2 H, d, $^3J_{HH}$ = 8.6 Hz, 2 CH of Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.01 (2 CH_2), 25.17 (4 CH_2), 30.90 (4 CH_2), 54.70 (2 NCH), 126.68 (2 CH of Ph), 128.89 (2 CH of Ph), 132.80 (CH of Ph), 141.42 (C_{ipso}-SO_2), 154.77 (C=O), 157.34 (C=N).

(23) (a) Ojima, I.; Akiba, K.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2559. (b) Inamoto, N.; Ojima, I. *J. Chem. Soc. D* **1970**, 1629. (c) Exner, O.; Jehlicka, V.; Dondoni, A. *Collect. Czech. Chem. Commun.* **1976**, *41*, 562. (d) Dondoni, A.; Battaglia, A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1475. (e) Ulrich, H.; Sayigh, A. A. R. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 520. (f) Sayigh, A. A. R.; Ulrich, H. US 3467651, **1969**; *Chem. Abstr.* **1969**, *71*, 112907.

(24) (a) Huisgen, R.; Herbig, K. *Chem. Ber.* **1967**, *100*, 1107. (b) Alizadeh, A.; Zohreh, N.; Zhu, L. G. *Synthesis* **2008**, 2073.